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Proposed Re-evaluation Decision PRVD2018-16

Clodinafop-propargyl and Its Associated End-use Products

Consultation Document

(publié aussi en français)

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Proposed Re-evaluation Decision

Under the authority of the *Pest Control Products Act*, all registered pesticides must be regularly re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental safety standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports, and other regulatory agencies. The PMRA applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Clodinafop-propargyl is a registered herbicide for use in western Canada on spring and durum wheat. It provides effective control of wild oats, which is one of the major weed problems for wheat growers in western Canada.

This document presents the proposed regulatory decision for the re-evaluation of clodinafop-propargyl including proposed risk mitigation measures to further protect human health and the environment, as well as the science evaluation on which the proposed decision was based. All products containing clodinafop-propargyl registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period, during which the public, including manufacturers and stakeholders, may submit written comments and additional information to the PMRA. The final re-evaluation decision will be published taking into consideration the comments and information received.

Outcome of Science Evaluation

With respect to human health, no risks of concern were identified for all uses of clodinafop-propargyl when used according to the proposed revised label directions.

Clodinafop-propargyl is not expected to pose risks of concern to the environment when used according to the proposed label directions, which include advisory statements and spray buffer zones.

Proposed Regulatory Decision for Clodinafop-propargyl

Under the authority of the *Pest Control Products Act* and based on the evaluation of currently available scientific information, products containing clodinafop-propargyl are being proposed for continued registration in Canada, with additional risk mitigation measures to further protect human health and the environment.

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment that must be followed by law. As a result of the re-evaluation of clodinafop-propargyl, further risk mitigation measures as summarized below for product labels are being proposed.

Human Health

- A plantback interval of 30 days.
- Preharvest intervals of 60 days for grain and straw, 30 days for hay, and seven days for forage.
- The standard spray drift statement will be standardized across all use product labels for label consistency.
- To protect mixer/loader/applicators:
  - Additional personal protective equipment (PPE) for mixers/loaders and ground boom applicators.
  - A closed mix/load system when handling more than 15 kilograms of active ingredient (kg a.i.) in a day.
- To protect workers entering treated sites: 12 hour restricted-entry interval (REI) for all activities.

Environment

- Standard hazard statements to inform users of the potential toxic effects on non-target terrestrial plants.
- A hazard statement to inform users of the presence of aromatic petroleum distillates and their toxicity to aquatic organisms.
- Advisory statement to inform users that residues of clodinafop-propargyl have the potential to leach to groundwater.
- To reduce the potential for runoff of clodinafop-propargyl to adjacent aquatic habitats, precautionary label statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecasted.
- To mitigate the potential exposure of clodinafop-propargyl to non-target organisms, addition of spray buffer zones to protect sensitive terrestrial and aquatic habitats from spray drift.

International Context

Clodinafop-propargyl is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including the European Union, the United States, and Australia.

No decision by an OECD member country to prohibit all uses of clodinafop-propargyl for health or environmental reasons has been identified.

Next Steps

All comments received during the 90-day public consultation period will be taken into consideration in preparation of re-evaluation decision document, which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with the PMRA's responses.

Additional Information Required

No additional information is required at this time.

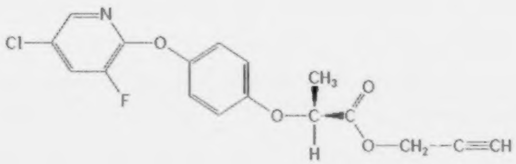
Science Evaluation

1.0 Introduction

Clodinafop-propargyl is an herbicide belonging to the aryloxyphenoxy-propionate family (Herbicide Resistance Action Committee Group A, Weed Science Society of America Group 1) used in western Canada on spring and durum wheat. Clodinafop-propargyl is absorbed by the leaves and rapidly translocated to the growing points of leaves and stems where it interferes with the production of fatty acids needed for plant growth in susceptible grassy weeds.

2.0 Technical Grade Active Ingredient

2.1 Identity

Common name	Clodinafop-propargyl
Function	Herbicide
Chemical Family	Aryloxyphenoxypropionate
Chemical name	
1 **International Union of Pure and Applied Chemistry (IUPAC)**	prop-2-ynyl (*R*)-2-[4-(5-chloro-3-fluoro-2-pyridyloxy)phenoxy]propionate
2 **Chemical Abstracts Service (CAS)**	2-propynyl (2*R*)-2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]propanoate
CAS Registry Number	105512-06-9
Molecular Formula	$C_{17}H_{13}ClFNO_4$
Structural Formula	
Molecular Weight	349.8

Registration Number	Purity of the Technical Grade Active Ingredient
24066	98%
27430	98%
29373	97.10%
29424	95%
29425	98%
29432	97.7%
30083	98.8%
30218	98.0%
30762	96.75%

2.2 Physical and Chemical Properties

Property	Result	Interpretation
Vapour pressure at 25°C	0.00319 mPa	*Low volatility, as classified by (Kennedy and Talbert, 1997)*
Ultraviolet/visible spectrum	λ_{max} = ~225 nm and 280 nm (No absorbance at $\lambda > 350$ nm)	*Low potential for direct phototransformation*
Solubility in water at 20–25°C	4.0 mg/L (pH 7)	*Low solubility in water*
n-Octanol/water partition coefficient	$\log K_{ow} = 3.9$	*Though parent has potential to bioaccumulate, it transforms rapidly to the acid which does not have a potential to bioaccumulate.*
Dissociation constant	N/A	*No dissociation at environmentally relevant pHs.*

Analytical data for certain sources of technical grade clodinafop-propargyl have been requested to confirm that the levels of impurities of toxicological concern such as dimethylformamide (DMF) are acceptable in certain products

2.3 Registered Uses

Appendix I lists all clodinafop-propargyl products that are registered under the authority of the *Pest Control Products Act*.

Appendix II lists all the uses for which clodinafop-propargyl is presently registered.

All uses were supported by the registrants at the time of initiation of re-evaluation and were, therefore, considered in the health and environmental risk assessments.

3.0 Human Health Assessment

3.1 Toxicology Summary

Clodinafop-propargyl belongs to the class of aryloxyphenoxypropionic herbicides. A detailed review of the toxicological database for clodinafop-propargyl was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The core studies were carried out in accordance with accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is acceptable and considered adequate to characterize the potential health effects of clodinafop-propargyl. The published scientific literature was also examined.

Based on radiolabel studies, in which rats were administered single or repeated oral gavage doses, clodinafop-propargyl was well absorbed from the intestinal tract. In these studies, clodinafop-propargyl was radiolabelled on either the U-phenyl, or pyridine portion of the molecule. Clodinafop-propargyl was widely distributed and tissue residues were highest in the fat, liver, kidneys and the reproductive organs eight hours post-dosing. Tissue residues were generally higher in males than females, likely as a result of a faster elimination rate in females than in males. More than 80% of the administered dose (AD) was excreted within the first 24 hours in females, while approximately 30% of the AD was excreted in males over the same period. Urine was the predominant route of excretion for both sexes, which accounted for up to 65% and 92% of the AD in males and females, respectively. Fecal excretion was approximately 25% and 6% of the AD in males and females, respectively. The elimination half-life ($t_{1/2}$) measured in the male rats was approximately 6.5 hours. Available data did not suggest a potential for accumulation in tissues following up to two-years of treatment.

Metabolism was extensive, with very low levels of unchanged clodinafop-propargyl detected in feces. Clodinafop was the major metabolite in urine, accounting for approximately 40% of the AD in males and 85% in females. Unchanged clodinafop-propargyl was not detected in urine. Other unidentified/uncharacterized minor metabolites in urine accounted for up to 5% of the AD. Clodinafop was the major metabolite in feces, accounting for approximately 10% of the AD in males and 3% in females. Six other minor metabolites were also extracted from feces, ranging from 0.3% to 1.4% of the AD. Of these, CGA-193468 was also identified as a major transformation product in the environment. All metabolites in fat were acylglycerides, the majority of which were hybrid di- and tri-acylglycerides (3.5 and 17% of the AD, respectively). In the liver, kidney and carcass, the metabolites observed were similar to those identified in the excreta and fat. Residues in expired air were negligible. The names of metabolites that were further characterized are presented in Appendix III, Table 1.

In rats and mice, clodinafop-propargyl was of low to slight acute oral toxicity. Clodinafop-propargyl was of low toxicity in acute dermal and inhalation toxicity studies in rats. Clinical signs of toxicity via all three dosing routes included increased piloerection, hunched posture, dyspnea, curved position, exophthalmos, and ruffled fur. Clodinafop-propargyl was non-irritating to the eyes and skin of rabbits, and was a dermal sensitizer in guinea pigs using the optimization test protocol.

Liver was the primary target organ of toxicity of clodinafop-propargyl following dietary administration in rats, mice, and dogs. Effects in the liver included increases in organ weight, and serum enzyme activities, and histopathological changes. In rodents, increased duration of dosing resulted in more pronounced histological changes in the liver. Other notable findings in repeat-dose studies included changes in clinical chemistry parameters, and at higher dose levels, decreased body weight, and altered organ weights. Testicular and thymic atrophy were observed in several studies in rodents. Additional findings in dogs included skin lesions. Short-term dermal exposure to clodinafop-propargyl resulted in clinical signs of toxicity (piloerection, hunched posture) at greater frequency and at lower dose levels in male versus female rats. In addition, altered organ (including liver) weights, and clinical chemistry parameters were noted.

The standard battery of genotoxicity studies was available for clodinafop-propargyl. Bacterial gene mutation tests were negative. A positive result was noted at cytotoxic doses in one of the three in vitro cytogenetics tests performed in cells derived from Chinese Hamsters. An in vitro cytogenetics test conducted with human lymphocytes was inconclusive. Clodinafop-propargyl did not induce unscheduled DNA synthesis. The in vivo mouse micronucleus assay was negative. The weight of evidence suggests that clodinafop-propargyl is not genotoxic.

In an 18-month dietary carcinogenicity study in mice, significant liver toxicity (elevated enzyme activities, increased weight, and histopathological changes) was noted. Increased incidences of testicular and thymic atrophy were observed in the high-dose group. Statistically significant (trend and pairwise analyses) increases in the incidence of hepatocellular adenomas as well as the combined incidence of hepatocellular adenomas and carcinomas were observed in high-dose male mice. These incidences exceeded historical control (HC) means and ranges, even though the HC data were obtained from studies of longer (24 month) duration. An increase in multiplicity of these tumour types was also noted. In female mice, the incidence of liver adenomas was marginally increased at the high-dose level; however, the incidence was within the HC range. A statistically significant (trend and pairwise analyses) increase in incidence of vascular tumours (hemangiomas and angiosarcomas) was also observed in high-dose female mice. Appropriate HC data were not available for vascular tumours.

The registrant proposed a peroxisome proliferator-activated receptor alpha (PPARα)-mediated mode of action (MOA) for the formation of liver tumours in mice. For this MOA, the key events are: activation of PPARα, followed by increased peroxisome numbers, increased cell proliferation, and increased pre-neoplastic foci ultimately leading to tumour formation. A series of mechanistic studies were conducted in rodents to support this MOA. The registrant also claimed that clodinafop-propargyl was structurally related to fibric acid derivative drugs (for example clofibrate, and bezafibrate) known to cause rodent liver tumours through a PPARα MOA.

A structure-activity relationship analysis performed by the United States Environmental Protection Agency indicated that two structural analogues (haloxyfop-methyl and diclofop-methyl) were found to induce liver tumours in mice.

The data provided for the key events were largely consistent with the established MOA for PPARα-mediated liver tumour formation. Activation of PPARα, increased peroxisome numbers, cell proliferation, and pre-neoplastic foci were noted in the available mechanistic, or short- and long-term studies in rodents with clodinafop-propargyl. Overall, the data suggested that the proposed MOA is plausible with some residual uncertainties remaining with regard to dose and temporal concordance for the key events, as well as the ability of clodinafop-propargyl to interact with, or activate PPARα. However, the weight of evidence for the MOA was sufficient to conclude that a linear low dose extrapolation (q_1*) approach to the cancer risk assessment for liver tumours may be overly conservative. For these reasons, a threshold approach for liver tumours was applied for the cancer risk assessment. No MOA data were provided for vascular tumours.

In a rat two-year dietary chronic/oncogenicity toxicity study, liver toxicity including increased weight and enzyme activities, and histopathological findings such as hepatocyte hypertrophy, fibrosis of liver capsule and parenchyma, hyperplasia, and necrosis, were observed at the two high-dose levels. Kidney toxicity was also observed at the same dose levels, which included histopathological findings such as tubular pigmentation, and chronic progressive nephropathy. Increased incidences of prostate adenoma and combined prostate adenomas and carcinomas, were noted in the high-dose males. These incidences were statistically significant (trend and pairwise) and exceeded the HC range. Examination of the individual animal data revealed a reduced time to tumour in these animals. Mortality patterns were not affected in the study. In high-dose female rats, an increased incidence of ovarian tubular adenomas was observed, which exceeded HC range. This incidence was also statistically significant (trend and pairwise). The incidence of ovarian tubular hyperplasia was also elevated in the same dose group. A pathology working group (PWG) conducted a re-read of the prostate and ovarian lesions. Treatment-related occurrence of the prostate tumours was confirmed in this re-read, but not the occurrence of the ovarian tumours. However, a statistically significantly increased incidence of granulosa-theca cell hyperplasia in the ovaries of the high-dose female rats was identified in the PWG re-read.

In a rat dietary two-generation reproductive toxicity study, increased liver weight, as well as decreased body weight, body weight gain, and food consumption were noted in the parental generation. In addition, at the highest dose level, hepatocyte hypertrophy, and kidney lesions (tubular and pelvis dilatation, hyaline casts, and pigment deposits in tubules) were noted. Effects in the offspring included decreased body weight and renal pelvis dilatation, and, at higher dose levels, reduced viability. The renal pelvis dilatation in offspring occurred at dose levels that did not produce toxicity in the maternal animals in this study, or in adult female rats in other studies in the database. Reproductive toxicity in this study, observed at the highest dose level, consisted of a marginally increased number of F_1 generation females with no pups delivered and a corresponding decrease in the gestation index for this group.

In a rat gavage developmental toxicity study, effects in maternal animals included marginally decreased body weight gain and food consumption. Developmental toxicity included reduced fetal body weights and increased incidences of a number of fetal variations at dose levels that did not produce maternal toxicity. The variations consisted of bilateral distension of the ureter and bilateral torsion of the ureter, hematoma to the head, and absent or incomplete ossification in various bones. In the rabbit developmental toxicity study, clodinafop-propargyl exposure caused death and significant clinical signs of toxicity at the two highest dose levels in the maternal animals.

Clinical signs of toxicity (laboured breathing, reduced activity, tremors, marked salivation, ataxia), occurred by the second day of dosing. There was no evidence of developmental toxicity.

There were some indications in the database that the endocrine system may be affected by clodinafop-propargyl. Pathological changes were observed in rat ovaries (theca cell hyperplasia), in rat prostate glands (tumours), and in the testes (atrophy) of rats and mice following repeated dietary administration. Decreased spermatogenesis was noted in the high-dose males of the 18-month mouse study. The mechanistic studies demonstrated induction of CYP450 enzymes that are also involved in steroidogenesis. Due to the age of the two-generation reproduction toxicity study, currently required endpoints, such as ovarian follicles, estrous cycle length and periodicity, or sperm parameters (motility and morphology), were not assessed.

Three neurotoxicity studies in rats were available for clodinafop-propargyl, including a gavage acute neurotoxicity study, a short-term dietary neurotoxicity study, and a dietary developmental neurotoxicity (DNT) study. In these studies, decreased body weight and body weight gain (including in the pup and maternal animals in the DNT study) were noted. In the gavage acute neurotoxicity study, an increased incidence of demyelination of proximal and distal tibial and sciatic nerves was observed in males. These findings did not occur in either the short-term or DNT study, which were conducted at lower doses. Altered motor activity levels were observed in the high-dose males of the acute and short-term neurotoxicity studies. In the DNT study, the motor activity assessment was deemed inadequate, mainly because the female control groups on PND60 did not show any habituation. Some limitations in reporting of the motor activity data were noted in all three studies. In addition, it was unclear whether motor activity included locomotor activity alone or total motor (locomotor and ambulatory) activity.

In the DNT study, decreased auditory startle reflex in male pups along with decreased piriform cortex thickness were noted at the high-dose level. In female pups of this group, decreased hippocampus length and width, and changes in the corpus callosum thickness were observed. These findings were noted at a dose level that produced marginal decreases in maternal body weight, and food consumption. Brain morphometry was initially conducted only in the control and high-dose animals of this study, but was conducted for the low- and mid-dose animals four years later. Due to a number of confounding variables which limited data interpretation, the morphometric analysis from the low- and mid-dose animals was deemed inadequate for hazard assessment purposes. No treatment-related effects were noted on measures of learning and memory as assessed in the Y maze.

The identities of characterized metabolites are presented in Appendix III, Table 1. Results of the toxicology studies conducted on laboratory animals with clodinafop-propargyl are summarized in Appendix III, Table 2. The toxicology reference values for use in the human health risk assessment are summarized in Appendix III, Table 3. The toxicological reference values are also applicable to other major transformation products, including clodinafop acid.

3.1.1 *Pest Control Products Act* (PCPA) Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the standard complement of required studies for risk assessment were available for clodinafop-propargyl, including oral gavage developmental toxicity studies in rats and rabbits and a dietary two-generation reproductive toxicity study in rats. Additionally, a dietary developmental neurotoxicity study in rats was available.

With respect to potential prenatal and postnatal toxicity, sensitivity of the young was noted in the reproductive toxicity study. Decreased body weight, and renal pelvis dilatation in pups were observed in this study at a dose level that did not cause toxicity to the maternal animals. However, since the incidence of renal pelvis dilatation was marginally increased compared to the control at this dose level, and this finding was not considered to be of a serious nature, the level of concern was low. Reduced pup viability was noted at higher dose levels in this study which was also toxic to the maternal animals. Sensitivity of the fetus was also noted in the rat developmental toxicity study, where dose-related increases in the incidences of bilateral torsion and distension of ureters of fetuses were observed. Although this effect occurred at dose levels that did not produce maternal toxicity in this study, this finding was not considered to be of a serious nature, and thus the level of concern was low. Increased incidences of incomplete or absent ossification in various skeletal regions were noted at higher dose levels in this study in the presence of minimal maternal toxicity. Significant maternal toxicity (mortality) was noted in the rabbit developmental toxicity study, but developmental toxicity was not observed. In the DNT study, at a maternally toxic dose level, changes in brain morphometry, consisting of decreased cortex thickness in male pups, and decreased hippocampus length and width, and changes in the corpus callosum thickness in female pups, were observed in the offspring. Decreased auditory startle reflex was also noted in male pups at this dose level. The supplemental examination of brain morphometry in the low- and mid-dose groups was considered unacceptable to further characterize the dose-response relationship of the brain morphometric findings.

Overall, the database is adequate for determining the sensitivity of the young. There was a low degree of concern for the findings in the rat reproductive and developmental toxicity studies. The brain morphometric changes, observed in pups in the DNT study, were considered serious endpoints, and were not characterized in the low- and mid-dose levels. However, slight evidence of maternal toxicity was observed at the same dose level and no effects on learning and memory were noted at any dose levels in this study. Additionally, auditory startle was not affected at low- and mid-dose levels. Therefore, the PCPA factor was reduced to threefold for scenarios in which this endpoint was used for risk assessment. For all other scenarios, the PCPA factor was reduced to onefold.

3.2 Dietary Exposure and Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Dietary exposure assessments are age-specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when exposure exceeds 100% of the reference value or the lifetime cancer risk estimate exceeds 1×10^{-6} (one-in-a-million). The PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute, chronic and cancer risk assessment procedures.

Sufficient information was available to adequately assess the dietary exposure and risk from clodinafop-propargyl. Acute and chronic dietary (food and drinking water) exposure and risk assessments for clodinafop-propargyl were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c) program which incorporates consumption data from the National Health and Nutrition Examination Survey/What We Eat in America for the years 2005-2010 available through the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics. Further details on the consumption data are available in the PMRA's Science Policy Note SPN 2014-01, *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments*. For more information on the dietary risk estimates or the residue chemistry information used in the dietary assessment, see Appendix IV.

3.2.1 Determination of Acute Reference Dose (ARfD)

All Populations

To estimate acute dietary risk (1 day), the DNT study with a NOAEL of 9 mg/kg bw/day was selected for risk assessment. At the LOAEL of 44 mg/kg bw/day, decreased auditory startle reflex, and changes in brain morphometry were observed. These effects could potentially result from a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to threefold. Thus, the composite assessment factor (CAF) is 300.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{9 \text{ mg/kg bw/day}}{300} = 0.03 \text{ mg/kg bw of clodinafop-propargyl}$$

3.2.2 Acute Dietary Exposure and Risk Assessment

The acute dietary risk was calculated considering the highest ingestion of residues of clodinafop-propargyl that would be likely on any one day, and using food and drinking water consumption and food and drinking water residue values. The expected intake of residues is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the estimated exposure is less than the ARfD, the acute dietary exposure is not of concern.

The assessment was conducted using the Canadian Maximum Residue Limit (MRL)/US Tolerance of 0.02 ppm for wheat commodities, and assuming all crops were 100% treated. Drinking water contribution to the exposure was accounted for by direct incorporation of the acute estimated environmental concentration (EEC) value obtained from water modelling (see Section 3.3), into the dietary exposure evaluation model (DEEM).

The acute dietary exposure estimates (from food and drinking water) at the 95th percentile were at or below 1% of the ARfD for the general population and all other subpopulations and thus, are not of concern.

3.2.3 Determination of Acceptable Daily Intake (ADI)

To estimate risk from repeat dietary exposure, the rat chronic toxicity/oncogenicity study with a NOAEL of 0.32 mg/kg bw/day was selected for risk assessment. At the LOAEL of 10.2/11.3 mg/kg bw/day, liver toxicity consisting of elevated enzyme activities, increased weight and histopathological lesions, and kidney toxicity consisting of increased incidence of chronic progressive nephropathy, and tubular degeneration were observed. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold. Thus, the CAF is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.3 \text{ mg/kg bw/day}}{100} = 0.003 \text{ mg/kg bw/day of clodinafop-propargyl}$$

The ADI provides a margin of 1666 to the dose level at which bilateral torsion and dilatation of the ureters were observed in the fetuses in the rat developmental toxicity study.

The ADI provides a margin of approximately 3700 to NOAEL for the liver tumours observed in the male mice of the 18-month oncogenicity study.

3.2.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated using average consumption of different foods and drinking water, and food and drinking water residue values. The estimated exposure was then compared to the ADI, which is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects. When the estimated exposure is less than the ADI, the chronic dietary exposure is not of concern.

The assessment was conducted using the Canadian Maximum Residue Limit (MRL)/American Tolerance of 0.02 ppm for wheat commodities, and assuming all crops were 100% treated. Drinking water contribution to the exposure was accounted for by direct incorporation of the chronic EEC value obtained from modelling (see Section 3.3) into DEEM.

The chronic dietary exposure estimates (from food and drinking water) were below 5% of the ADI for the general population and all other subpopulations and thus, are not of concern.

3.2.5 Cancer Assessment

Treatment-related increases in the incidences of liver tumours in males and vascular tumours in females were noted in the mouse carcinogenicity study. The MOA of PPARα-mediated hepatocarcinogenesis was considered plausible, but with some uncertainties. However, a linear, low-dose extrapolation approach using the liver tumours was considered overly conservative. No MOA data was provided for vascular tumours. In the rat two-year carcinogenicity study, treatment-related increased incidences of ovarian and prostate tumours were observed. The occurrence of the prostate tumours was confirmed in the PWG re-read; however, the ovarian tumours were downgraded to hyperplastic lesions. Therefore, a linear, low-dose extrapolation approach for cancer risk assessment was deemed appropriate for the prostate tumours. The cancer unit risk value (q_1*) for the incidence of prostate adenomas/carcinomas combined in male rats from the PWG re-read report is 0.0302 $(\text{mg/kg bw/day})^{-1}$. This cancer unit risk (q_1*) is protective of the vascular tumours (as well as ovarian tumours noted in the original study report). The cancer potency factor was considered relevant to all routes of exposure.

3.2.6 Cancer Dietary Exposure and Risk Assessment

The cancer dietary risk was calculated using average consumption of different foods and drinking water and food and drinking water residue values. The estimated chronic exposure was then compared to the cancer potency factor (q_1*). A lifetime cancer risk that is equal or below 1×10^{-6} (one-in-a million) does not indicate a risk of concern for the general population when exposure occurs through pesticide residues in or on food, or to otherwise unintentionally exposed persons.

The assessment was conducted using the anticipated residues (from field trials) for wheat commodities, and domestic percent crop treated information. Drinking water contribution to the exposure was accounted for by direct incorporation of the average EEC value obtained from modelling (see Section 3.3) into DEEM.

Based on the q_1* approach, the lifetime cancer dietary risk estimate (from food and drinking water) is approximately 1×10^{-6} for the general population and thus, is not of concern.

3.3 Exposure from Drinking Water

Residues of clodinafop-propargyl in potential drinking water sources were estimated from water modelling. Toxicology endpoint selection for residential and occupational exposure may be found in Appendix V (including estimated concentrations in drinking water sources and water monitoring data).

3.3.1 Concentrations in Drinking Water

EECs of clodinafop-propargyl were calculated using the Pesticides in Water Calculator (PWC) model. Two use patterns were modelled: 1) a single application rate of 70.2 g a.i./ha for use on spring wheat in western Canada and 2) a single application rate of 30 g a.i./ha for use on winter wheat across Canada and on spring wheat in eastern Canada. Modelling used initial application dates between mid-May and late August. EECs in groundwater were calculated by selecting the highest EEC from several selected scenarios representing spring and winter wheat grown in different regions of Canada. All scenarios were run for either 50 or 100 years.

The highest groundwater daily EEC value of 1.64 ppb and groundwater yearly average EEC value of 1.51 ppb were used in acute and chronic (cancer and non-cancer) exposure assessments, respectively.

3.3.2 Drinking Water Exposure and Risk Assessment

Drinking water exposure estimates were combined with food exposure estimates, with EEC point estimates incorporated directly in the dietary (food and drinking water) assessments. No risks of concern were identified. Please refer to Sections 3.2.2 and 3.2.4 for details.

3.4 Occupational and Non-Occupational Exposure and Risk Assessment

Non-Cancer Risk Assessment

Occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

Cancer Risk Assessment

The cancer risk is determined by calculating the lifetime average daily dose (LADD) from dermal, inhalation and/or oral exposure. The LADD is multiplied by the cancer potency factor (q_1*) to obtain a lifetime cancer risk estimate, which is a measurement of probability. A lifetime cancer risk in the range of 1×10^{-5} in worker populations and in the range of 1×10^{-6} in residential populations is generally acceptable.

3.4.1.1 Short- and Intermediate-term Dermal and Inhalation Exposure

For short-, and intermediate-term occupational exposures via the dermal and inhalation routes, the offspring NOAEL of 0.41 mg/kg bw/day from the two-generation reproduction toxicity study in rats was selected for risk assessment. Increased incidences of unilateral/bilateral dilatation of the renal pelvis in F_2 pups and decreased pup (and litter) weight during late lactation in F_1 pups were noted in the F_1 generation. The target MOE for these scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all worker populations including women who may be pregnant or nursing. Although a 28-day dermal toxicity study in rats was available, it was not chosen for endpoint selection since the design of the study does not allow for the assessment of the relevant endpoint of concern, dilatation of renal pelvis and decreased body weight in pups. A short-term inhalation study was not available.

3.4.1.2 Cancer Assessment

Treatment-related increases in the incidences of liver tumours in males and vascular tumours in females were noted in the mouse carcinogenicity study. The MOA of PPARα-mediated hepatocarcinogenesis was considered plausible, but with some uncertainties. However, a linear, low-dose extrapolation approach using the liver tumours was considered overly conservative. No MOA data was provided for vascular tumours. In the rat two-year carcinogenicity study, treatment-related increased incidences of ovarian and prostate tumours were observed. The occurrence of the prostate tumours was confirmed in the PWG re-read; however, the ovarian tumours were downgraded to hyperplastic lesions. Therefore, a linear, low-dose extrapolation approach for cancer risk assessment was deemed appropriate for the prostate tumours. The cancer unit risk value (q_1^*) for the incidence of prostate adenomas/carcinomas combined in male rats from the PWG re-read report is 0.0302 (mg/kg bw/day)$^{-1}$. This cancer unit risk (q_1^*) is protective of the vascular tumours (as well as ovarian tumours noted in the original study report). The cancer potency factor was considered relevant to all routes of exposure.

3.4.1.3 Dermal Absorption

A rat in vivo study (PMRA# 1682368) and a rat in vitro and human in vitro study (PMRA# 2670883) were submitted to the PMRA for clodinafop-propargyl. These studies were considered by the PMRA to refine the dermal absorption value for clodinafop-propargyl. The rat in vivo study (PMRA# 1682368) contained no major study limitations and was considered when determining a dermal absorption value for clodinafop-propargyl.

A dermal absorption value of 42% was determined for clodinafop-propargyl based on the results of the rat in vivo study (PMRA# 1682368). This dermal absorption value is supported by the in vitro study (PMRA# 2670883), where a dermal absorption of 38% was observed for the low dose from the human skin sample, as well as the observations from toxicological studies. A dermal absorption value of 42% is not expected to underestimate exposure.

3.4.2 Non-Occupational Exposure and Risk Assessment

A residential assessment was not required since there are no domestic-class products containing clodinafop-propargyl and, based on the registered use pattern, commercial application to residential areas is not expected.

A standardized statement is proposed to prohibit application when there is potential drift to areas of human habitation or areas of human activity. The proposed label statement is listed in Appendix IX.

3.4.3 Occupational Exposure and Risk Assessment

There is potential for exposure to clodinafop-propargyl through mixing, loading, or applying the pesticide, and when entering a treated site to conduct postapplication activities such as scouting.

3.4.3.1 Mixer, Loader, and Applicator Exposure and Risk Assessment

There are potential exposures to mixers, loaders, and applicators. The following scenarios were assessed:

- Open mixing/loading (liquids)
- Closed mixing/loading (liquids)
- Open cab groundboom liquid application to spring and durum wheat
- Open cockpit aerial liquid application to spring and durum wheat

Based on the number of applications and the timing of application, workers applying clodinafop-propargyl would generally have a short (<30 days) duration of exposure. For the cancer assessment, the LADD was calculated assuming 40 years of exposure (that is, a career in agriculture of 40 years) over a 78 year lifetime. Farmer and custom applicators were assumed to be exposed for up to a total of 30 days per year based on the number of applications per year.

Handler exposure was estimated based on the following personal protection:

- Mid-level PPE: Cotton coveralls over long sleeved shirt, long pants, and chemical resistant gloves.

No appropriate chemical-specific handler exposure data were available for clodinafop-propargyl; therefore, dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database (PHED) Version 1.1, and the Agricultural Handler Exposure Task Force (AHETF).

Dermal and inhalation exposures were estimated using data from the PHED and AHETF. The PHED and AHETF are compilations of generic mixer/loader/applicator passive dosimetry data which are used for scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of PPE. The AHETF was formed in 2001 with the objective of providing more up-to-date generic exposure studies compared to the PHED studies.

Mixer/loader/applicator exposure estimates are based on the best available data at this time. Route specific MOEs for mixer/loader and applicators for agricultural crops are outlined in Appendix VI, Table 1. Calculated dermal, inhalation, and combined (total exposure from dermal and inhalation routes) MOEs for mixer/loaders and applicators of clodinafop-propargyl exceeded target MOEs for all scenarios when handling less than 15.1 kg a.i./day. When handling more than 15.1kg a.i./day, a closed mix/load system is proposed in order to achieve target MOEs.

For all uses, based on proposed label PPE recommendations and current application rates, the calculated cancer risk estimates are below 1×10^{-5} and are not of concern (Appendix VI, Table 2).

3.4.3.2 Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considered exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact (for example, scouting). Based on the use pattern, there is potential for short-term (<30 days) postapplication exposure to clodinafop-propargyl residues for workers.

Activity-specific transfer coefficients (TC) from the Agricultural Re-entry Task Force (ARTF) were used to estimate postapplication exposure resulting from contact with treated foliage at various times after application. The TC is a factor that relates worker exposure to dislodgeable residues. TCs are specific to a given crop and activity combination (for example, hand harvesting apples, scouting late season corn) and reflect standard clothing worn by adult workers. Postapplication exposure activities include: scouting and weeding.

Dislodgeable foliar residues (DFR) refer to the amount of residue that can be dislodged or transferred from a surface, such as the leaves of a plant. There were no chemical specific DFR studies submitted to the PMRA for the re-evaluation of clodinafop-propargyl; therefore the following defaults were used:

- A default peak value of 25% of the application rate with a dissipation rate of 10% per day was used for DFR.

For workers entering a treated site, restricted-entry intervals (REIs) are calculated to determine the minimum length of time required before people can safely enter after application. An REI is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures above the target MOE.

The PMRA is primarily concerned with the potential for dermal exposure for workers performing postapplication activities in crops treated with a foliar spray. Based on the vapour pressure of clodinafop-propargyl, inhalation exposure is not likely to be of concern provided that the minimum 12-hour REI is followed.

Calculated dermal MOEs for worker postapplication exposure to clodinafop-propargyl in commercial crops exceeded target MOEs and are not of concern. REIs were set at the standard minimum value of 12 hours for all postapplication activities. The postapplication exposure assessment is outlined in Appendix VI, Table 3.

For all post application activities, based on proposed label PPE recommendations and current dislodgeable foliar residue dissipation rates, the calculated cancer risk estimates are below 1 × 10^{-5} and are not of concern (Appendix VI, Table 4).

3.5 Aggregate Exposure and Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

For clodinafop-propargyl, the aggregate assessment consisted of combining food and drinking water exposure only (for which there were no risks of concern, see Sections 3.2.2 and 3.2.4), since residential exposure is not expected to occur.

3.6 Cumulative Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Clodinafop-propargyl belongs to a group of chemicals classified as aryloxyphenoxypropionic herbicides. For the current re-evaluation, the PMRA did not identify information indicating that clodinafop-propargyl shares a common mechanism of toxicity with other pest control products. Additionally, clodinafop-propargyl does not appear to produce a toxic metabolite produced by other pest control products. At this time a cumulative assessment is not required.

3.7 Incident Reports

As of 16 January 2018, there were seven human incidents involving clodinafop-propargyl. All incidents were considered to be related to the reported product. Exposure to a product containing clodinafop-propargyl occurred either during mixing, loading or applying a product or as a result of drift from an application site. The severity of the reported effects was mainly minor. Overall, given the low severity and frequency of clodinafop-propargyl incidents, no additional mitigation measures specific to health are proposed as a result of the incident reports.

4.0 Environmental Assessment

4.1 Fate and Behaviour in the Environment

A summary of environmental fate data for combined residues of clodinafop-propargyl and CGA 193469 is presented in Appendix VII: Table 1.

Clodinafop-propargyl breaks down rapidly (DT_{50} of less than 2 days) in soil and in water. Hydrolysis is an important route of dissipation for clodinafop-propargyl, especially in alkaline conditions. Photolysis is not an important route of dissipation in soil, but is an important route of transformation in the upper layers of water bodies that receive sunlight. Biotransformation on land and water is an important route of dissipation of clodinafop-propargyl. Under aerobic conditions in soil and in water, clodinafop-propargyl degrades into three major transformation products (CGA 193469, CGA 30237 and CGA 193468). Degradation occurs simultaneously with evolution of carbon dioxide and formation of non-extractable residues (NER) attached to the organic matter of the soil. Up to 61.8% of the applied radioactivity in laboratory studies were retained as NER. Under anaerobic conditions, degradation proceeds in a similar pattern but at a much slower rate. Formation of carbon dioxide and NER are also greatly reduced under anaerobic conditions. Clodinafop-propargyl and its transformation products are non-persistent to moderately persistent in soil and slightly persistent to persistent in water based on laboratory studies.

Depending on soil type, the affinity of clodinafop-propargyl to attach to soil organic matter varies significantly (K_d : 0.17-352). The transformation products (CGA 193469, CGA 302371 and CGA 193468) have low affinity to bind to soil organic matter. According to the classification of Cohen *et al.* 1984, clodinafop-propargyl is classified as slightly mobile to very highly mobile in the environment; while CGA 193469 and CGA 302371 are classified as highly mobile to very highly mobile and CGA 193468 is classified as having low to moderate mobility. Based on the method of Gustafson (1989), the groundwater ubiquity score (GUS) for clodinafop-propargyl (0.55–3.68) classifies it as a non-leacher to leacher, while the GUS for the transformation product CGA 193469 (2.23 to 4.35) classifies it as a borderline leacher to leacher. Clodinafop-propargyl transforms rapidly into CGA 193469 and is therefore not expected to leach in the environment. The transformation product CGA 193469 meets most of the criteria for leaching according to the criteria of Cohen *et al.* (1984), (Appendix VII: Tables 2a and 2b) indicating a potential to leach to groundwater. CGA 193469 is very soluble in water (>5600 mg/L). The results of adsorption/desorption studies, water modelling, criteria of Cohen *et al.* (1984) for leaching and the GUS all suggest that CGA 193469 has a potential to leach.

Field trials conducted in Alberta and North Dakota indicate that clodinafop-propargyl and its transformation products are not expected to build up in soil or be carried over in important amounts into the next growing season. Under field conditions, clodinafop-propargyl and the transformation product CGA 193469 remained mostly in the top 15-cm soil layer, with CGA 193469 being measured occasionally at depths down to 30 cm. This observation is consistent with the results of the laboratory studies and predictions of GUS and Cohen *et al.* which indicate a potential for CGA 193469 to leach. The physicochemical properties of CGA 193469 (dissociation constant of 2.91 and water solubility of >5600 mg/L) also indicate that CGA 193469 may be expected to leach to groundwater.

Clodinafop-propargyl has a vapour pressure of 3.19×10^{-6} Pa at 25 °C and is not considered to be volatile. The calculated Henry's Law Constant of 2.8×10^{-4} Pa m³/mol indicates that volatilization from moist soil and water surfaces is not expected. The transformation product CGA 193469 has a vapour pressure of 7×10^{-07} Pa and a calculated Henry's law constant of < 3.9×10^{-10} Pa m³/mol. It is also not expected to volatilize from moist soil and water surfaces.

Clodinafop-propargyl has a log K_{ow} of 3.9 which indicates that it may bioaccumulate if it persists. However, this is not expected due to its rapid transformation to CGA 193469. CGA 193469 is not expected to bioaccumulate based on a log K_{ow} of -0.44.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. EECs are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. EECs are presented in Appendix VIII: Table 1 to Table 3. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e., protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value [RQ = exposure/(toxicity × uncertainty factor – if applicable)], and the risk quotient is then compared to the level of concern (LOC; Appendix VII, Table 3).

If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

A summary of toxicity data for clodianfop-propargyl and its transformation products CGA 193469, CGA 302371, CGA 193468 and end-use products is presented in Appendix VII, Table 4.

4.2.1 Risks to Terrestrial Organisms

A summary of endpoints, EECs and risk quotients for terrestrial organisms are presented in Appendix VII, Tables 4 to 6. For assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following use of clodinafop-propargyl.

Clodianfop-propargyl and its soil transformation products CGA 193469, CGA 193468 and CGA 302371 were found to be non-toxic to earthworms on acute basis. Clodinafop-propargyl was found to be relatively non-toxic to bees on an acute oral and acute contact basis. A larval bee toxicity study was not available at the time of this review. A larval bee toxicity study is not required at this time due to the fact that clodinafop-propargyl is an herbicide and its mode of action (inhibition of plant growth enzyme) is unlikely to result in bee toxicity. In addition, clodinafop-propargyl exhibits low toxicity to bees and there are no incident reports related to clodinafop-propargyl and bees.

Clodinafop-propargyl and CGA 193469 were found to have adverse effects on the beneficial arthropod species *Typhlodromus pyri* and *Aphidius rhopalosiphi* when exposed to dried spray layer (on glass plates). The level of concern (LOC=2) was exceeded, with risk quotients (RQ) ranging from 2.27 to 3.51 for *Typhlodromus pyri* and 11.18–22.36 for *Aphidius rhopalosiphi*. In extended laboratory studies, the level of concern (LOC=1) was not exceeded. RQ values were < 0.52 for *Aphidius rhopalosiphi* and < 0.78 for *Typhlodromus pyri*. No effects were observed in *Aleochara bilineata* following exposure to clodinafop-propargyl in an end-use product. Based on the results of the extended laboratory tests, use of clodinafop-propargyl is expected to pose negligible risks to beneficial arthropods under more realistic conditions.

Clodinafop-propargyl was found to be moderately to slightly toxic to birds on acute basis and practically non-toxic to small wild mammals, on acute basis. Both the acute oral and dietary endpoints were used to calculate screening level risk quotients for birds and mammals. No risks of concern were identified at the screening level for birds. There was a slight reproductive risk identified to small wild mammals feeding on short grass, long grass, broadleaf plants and insects at the screening level when considering maximum nomogram residues (RQ=1.02–1.99) on field. Off field, reproductive risks to small wild mammals were negligible (Appendix VII, Tables 7a and 7b).

Considering that clodinafop-propargyl is used as an herbicide, it is not unexpected that risks to terrestrial vascular plants from the maximum single application rate of 70.2 g a.i./ha to wheat were identified. Data for toxicity to terrestrial plants were reviewed for clodinafop-propargyl in formulation with the safener, cloquintocet-mexyl, and for the breakdown product CGA 193469. Corn, oat and ryegrass were the most sensitive monocot species to clodinafop-propargyl in the formulation with risk quotients of 13, 4.7 and 2 based on phytotoxic effects and shoot dry weight in vegetative vigour and seedling emergence tests. The most sensitive species to CGA 193469 were ryegrass and corn, with risk quotients of 4.1 and 2 based on reduced biomass in seedling emergence and vegetative vigour tests. Terrestrial spray buffer zones are proposed as a required mitigation measure to protect sensitive non-target plants.

4.2.2 Risks to Aquatic Organisms

A summary of endpoints, EECs, and risk quotients for aquatic organisms are presented in Appendix VII, Tables 4 to 6.

Based on available data, clodinafop-propargyl, its transformation products (CGA 193469, CGA 302371, CGA 193468) and the end-use products tested are slightly toxic to very highly toxic to freshwater invertebrates and moderately to highly-toxic to freshwater and marine/estuarine fish. At the screening level, the LOC was not exceeded for any aquatic organisms other than amphibians (RQ=2.2–3.3) (Appendix VII, Table 5). Clodinafop-propargyl , its transformation products (CGA 193469, CGA 302371 and CGA 193468) and the end-use products tested are not expected to pose risks of concern to freshwater fish, aquatic invertebrates, freshwater algae, freshwater plants, marine invertebrates or marine fish. The risks to amphibians, characterised further in (Appendix VII, Table 6), can be mitigated with a proposed mandatory one-metre spray buffer zone.

4.3 Incident Reports – Environment

As of 15 August 2016, one Canadian incident and two American incidents associated with the use of clodinafop-propargyl on terrestrial plants were reported in the United States Environmental Protection Agency Ecological Incident Informationm System database. Two of these incidents were classified as "possibly" the result of clodinafop-propargyl use, while the third incident was classified as "probably" the result of accidental misuse of a clodinafop-propargyl product. No additional incidents have been reported as of 16 January 2018 in Canada.

5.0 Value

5.1 Value of clodinafop-propargyl

Clodinafop-propargyl is a herbicide registered exclusively for use on wheat (spring and durum) to control a wide range of grass weeds. It is usually applied as a post-emergence in-crop treatment when a pre-seeding burn off with a glyphosate product does not provide adequate grass weed control or a new flush of grass weeds are emerging. It is also often used as a tankmix partner with a wide range of post-emergence broadleaf herbicides, for one-pass control of both grass and broadleaf weeds. Thus, clodinafop-propargyl is an integral component of an overall weed management program in spring and durum wheat.

Clodinafop-propargyl provides effective control of wild oats, which is one of the major weed problems for wheat growers in western Canada. Among all grass herbicides registered for use on wheat, clodinafop-propargyl has the most extensive list of broadleaf herbicide tank-mix partners which provide growers greater flexibility to choose the weed control program based on their actual needs.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

In accordance with the PMRA Regulatory Directive DIR99-03, the assessment of clodinafop-propargyl and its transformation products against Track 1 criteria of Toxic Substances Management Policy (TSMP) under Canadian Environmental Protection Act was conducted. It was determined that:

- Clodinafop-propargyl does not meet all Track 1 criteria, and is not considered a Track 1 substance (refer to Appendix VII, Table 8),
- Clodinafop-propargyl does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical grade active ingredient and formulants and contaminants in the end-use products are compared against the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern maintained in the Canada Gazette. The list is used as described in the PMRA Notice of Intent NOI2005-01 and is based on existing policies and regulations including DIR99-03; and DIR2006-02, and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the Canadian Environmental Protection Act (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

Technical grade clodinafop-propargyl does not contain any formulants or contaminants of health or environmental concern identified in the Canada Gazette. However, with the exception of registered products PCP# 29089, 29614, 30341 and 30426, all the other end-use products of clodinafop-propargyl do contain an aromatic petroleum distillate. Therefore, the label for the end-use products that contain aromatic petroleum distillates must include the statement: "This product contains aromatic petroleum distillates that are toxic to aquatic organisms."

Use of clodinafop-propargyl in formulation with cloquintocet-mexyl is not expected to produce synergistic effects on non-target organisms.

The use of formulants in registered pest control products is assessed on an ongoing basis through the PMRA formulant initiatives and Regulatory Directive DIR2006-02 (PMRA Formulants Policy).

7.0 Conclusions

Clodinafop-propargyl is a widely used grass herbicide in spring and durum wheat. It provides effective control of wild oats, which is one of the major weed problems for wheat growers across Canada. It can be tank mixed with a wide range of broadleaf herbicides to broaden weed control spectrum and reduce application passes.

With respect to human health, no risks of concern were identified for the supported uses of clodinafop-propargyl when used according to the proposed revised label directions.

Clodinafop-propargyl breaks down to CGA 193469 rapidly in soil and water. The transformation product CGA 193469 is not expected to persist in the environment and produces two additional major transformation products in the environment (CGA 302371 and CGA 193468), neither of which is expected to persist in the environment. Clodinafop-propargyl, CGA 193469, CGA 302371 and CGA 193468 are not expected to build up in soil and be carried over into the next growing season. Clodinafop-propargyl and the transformation products CGA 193469 and CGA 302371 are expected to move downward through the soil and have the potential to enter and contaminate groundwater. CGA 193469 is very soluble in water (>5600 mg/L) and slightly persistent in aquatic environments. Based on modelling, the criteria of Cohen *et al.*, (1981), the groundwater ubiquity score (Gustafson, 1989) and occasional detections in the field, CGA 193469 has a potential to leach. Clodinafop-propargyl and CGA 193469 are unlikely to accumulate in animal tissues.

In the terrestrial environment, risks to earthworms, beneficial arthropods, birds, mammals, bees, are not expected to be of concern. Risks of concern were identified for plants. Spray buffer zones are required to reduce exposure to sensitive non-target terrestrial plants.

In the aquatic environment, risks to fish, aquatic invertebrates, algae, aquatic plants and marine invertebrate and fish are not expected to be of concern. A potential risk to amphibians was identified. A one-meter spray buffer zone is required to mitigate risks to amphibians.

List of Abbreviations

µg	micrograms
µm	micrometre
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
abs	absolute
ACO	acyl CoA oxidase
AD	administered dose
ADD	Absorbed Daily Dose
ADI	acceptable daily intake
a.e.	acid equivalent
AHETF	Agricultural Handlers Exposure Task Force
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARfD	acute reference dose
ARTF	Agricultural Reentry Task Force
AST	aspartate aminotransferase
atm	atmosphere
ATPD	area treated per day
AUC	area under the curve
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	chemical abstracts service
CGA	clodinafop acid
CI	confidence Interval
cm	centimetres
cm^2	centimeters squared
cm^2/hr	centimeters squared per hour
CoA	Coenzyme A
CPN	chronic progressive nephropathy
DA	dermal absorption
DACO	data code
DAR	draft assessment report
DEEM	Dietary Exposure Evaluation Model
DFR	dislodgeable foliar residue
DMF	dimethylformamide
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
DT$_{50}$	dissipation time 50% (the time required to observe a 50% decline in concentration)
DT$_{75}$	dissipation time 75% (the time required to observe a 75% decline in concentration)
DT$_{90}$	dissipation time 90% (the time required to observe a 90% decline in concentration)
dw	dry weight
E_bC_{50}	effective concentration for 50% reduction in biomass growth
E_rC_{50}	effective concentration for 50% reduction in growth rate

EC_{05}	effective concentration on 5% of the population
EC_{10}	effective concentration on 10% of the population
EC_{25}	effective concentration on 25% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
EFSA	European food safety authority
ER_{25}	effective rate on 25% of the population
ER_{50}	effective rate on 50% of the population
F_1	first generation
F_2	second generation
FC	food consumption
FCID™	Food Commodity Intake Database™
FIR	food ingestion rate
FOB	functional observational battery
g	gram(s)
GD	gestation day
h	hour
ha	hectare
HC	historical control
HCD	historical control data
HPLC	high performance liquid chromatography
hr	hour
HRAC	Herbicide Resistance Action Committee
IUPAC	International Union of Pure and Applied Chemistry
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	octanol-water partition coefficient
kg	kilogram(s)
L	litre(s)
LADD	lifetime average daily dose
LC_{50}	lethal concentration to 50%
LD	lactation day
LD_{50}	lethal dose to 50%
LDH	lactate dehydrogenase
LOAEL	lowest observed adverse effect level
LOEC	lowest observed effect concentration
LOD	limit of detection
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m	metre(s)
M/L/A	mixer, loader and applicator
MAS	maximum average score for 24, 48 and 72 hours
max	maximum
mg	milligram(s)
min	minutes
MIS	maximum irritation score
mL	millilitre
mmol	millimole
MnPCE	micronucleated polychromatic erythrocyte
MOA	mode of action

MOE	margin of exposure
MRL	Maximum Residue Limit
MS	mass spectrometry
N/A	not applicable
NER	non-extractible residue
NOAEL	no observed adverse effect level
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
N/R	not required
OC	organic carbon content
OM	organic matter content
P	parental generation
Pa	Pascal
PCPA	Pest Control Product Act
PHED	Pesticide Handlers Exposure Database
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPARα	peroxisome proliferator-activated receptor alpha
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
PWG	pathology working group
q1*	cancer potency factor
RAR	renewal assessment report
RBC	red blood cells
REI	restricted-entry interval
rel	relative
SOP	standard operating procedures
SPF	specific pathogen free
SPN	Science Policy Note
$t_{1/2}$	half-life
TC	transfer coefficient
TSMP	Toxic Substances Management Policy
Ue	Unextracted
USEPA	United States Environmental Protection Agency
WBC	white blood cells

Appendix I Products containing clodinafop-propargyl that are registered in Canada excluding discontinued products or products with a submission for discontinuation as of 31 December 2017, based upon the PMRA's Electronic Pesticide Regulatory System (e-PRS) database

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Net Content	Guarantee
29495	C	Adama Agricultural Solutions Canada LTD	Mana Ladder 240 EC	Emulsifiable Concentrate or Emulsion	1–1050 L	240 g/L
30428	C		Cadillac		1–1050 L	240 g/L
32497	C		Ladder All In		4–1050 L	80 g/L
32539	C		Cadillac One		4–1050 L	80 g/L
30137	C	Agri Star Canada ULC	Slam'r Clodinafop Herbicide		1.84L, 3.68L, 4.7L, 14L, 15L, 55L, 200L, 450L, 1100L, Bulk	240 g/L
31053	C		Slam'r Herbicide		1–1100 L, Bulk	240 g/L
29614	C	Arysta Lifescience North America, LLC	Nextstep NG Herbicide		9.46 L, 1 L - Bulk	60 g/L
29299	C	E.I. Du Pont Canada Company	Harmony Grass		1 L - Bulk	128 g/L
31689	C		Harmony Grass 240 EC Herbicide		1 L - Bulk	240 g/L
30445	C	FMC Corporation	Bullwhip 240EC Herbicide		250 ml - Bulk	240 g/L
29526	C	Interprovincial Cooperative Limited	Legend A		1.84 – 1100 L	240 g/L
29711	C	Newagco Inc.	Mpower Aurora® Clodinafop Herbicide		1.84L, 3.68L, 4.7L, 14L, 15L, 55L, 200L, 450L, 1100L, Bulk	240 g/L
30949	C		Mpower Aurora-I Clodinafop Herbicide		250 ml - Bulk	240 g/L
29172	C	Nufarm Agriculture Inc.	Signal Herbicide		1.84 L - Bulk	240 g/L
29962	C		Nufarm Clodinafop Herbicide		1 L - Bulk	240 g/L
30168	C		Nufarm Signal Herbicide		1 L - Bulk	240 g/L
31434	C		Signal F Herbicide		1 L - Bulk	112 g/L (+ fluoxypyr 217 g/L)
31261	C	Productierra	Foax Herbicide		1.84L, 3.68L, 4.7L, 14L, 15L, 55L, 200L, 450L, 1100L, Bulk	240 g/L
24067	C	Syngenta Canada Inc.	Horizon 240EC Herbicide	Emulsifiable Concentrate or	1.84 L - Bulk	240 g/L

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Net Content	Guarantee
24076	C		Horizon 240EC Herbicide (component of horizon herbicide tank mix)	Emulsion	1.84 L, 3.68L, 4 L, 4.7 L, 8L	240 g/L
29089	C		Horizon NG Herbicide		9.46 L, 1 L - Bulk	60 g/L
29202	C		Harmony Grass 128EC Herbicide		1 L - Bulk	128 g/L
29855	C		Traxos Herbicide		1 L - Bulk	25 g/L (+ pinoxaden 25 g/L)
30341	C		Foothills NG Herbicide		1 L - Bulk	60 g/L
31674	C		Traxos®two Grass Component		1 L - Bulk	25 g/L (+ pinoxaden 25 g/L)
30743	C	United Phosphorus Inc.	Current 240 EC Herbicide		1.84L, 3.68L, 4.7L, 14L, 15L, 55L, 450L, 1100L, Bulk	240 g/L
31157	M		Current 240 EC MUP Herbicide		15L – 1100 L, Bulk	240 g/L
29373	T	Adama Agricultural Solutions Canada LTD	Mana Clodinafop-Propargyl Technical	Dust	50–1050 kg	97.1%
29425	T	Agrogill Chemicals PTY LTD	Clodinafop-propargyl Agrogill Technical Grade Active Ingredient	Solid	50 kg	98.0%
30083	T	FMC Corporation	FMC Clodinafop-Propargyl Technical Herbicide		250 g to Bulk	98.8%
29424	T	Newagco Inc.	Newagco Clodinafop-Propargyl Herbicide Technical		50–1000 kg	95.2%
30762	T	Productierra	Technical Clodinafop Herbicide		50–1000 kg	96.75%
30218	T	Sinon USA Inc.	Clodinafop-propargyl Sinon Technical Active Ingredient		25–250 kg	98.0%
24066	T	Syngenta Canada Inc.	Clodinafop-propargyl Technical Herbicide	Dust or Powder	Bulk	98%
27430	T		Clodinafop-propargyl Technical Active Ingredient		Bulk	98%
29432	T	United Phosphorus Inc.	UPI Clodinafop-propargyl Technical Herbicide		50 kg	97.7%

Appendix II Registered Commercial Class uses of clodinafop-propargyl in Canada as of 31 December 2017. Uses from discontinued products or products with a submission for discontinuation are excluded[1]

Use-Site Category	Sites[2]	Weeds	Application Method and Equipment	Maximum Application Rate (g a.i./ha)	
				Single[4]	Cumulative Per Year[4]
Terrestrial Feed crops Terrestrial Food crops	Wheat (spring and durum) Prairie provinces and Peace River, Okanagan and Creston flats of British Columbia only	Grassy weeds	Ground and aerial	70.2	70.2

1. The maximum number of applications is once per year.
2. Sites are as either stated on the label or interpreted by the PMRA so as to achieve consistency in naming.

Appendix III Toxicological Information for Health Risk Assessment

Table 1 Select Clodinafop-propargyl Metabolites

Common Name (Other names)	Chemical Name (IUPAC)
Clodinafop acid (CGA193469)	(R)-2[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-propanoic acid
CGA 214111	2-(4-hydroxy-phenoxy)-propionic acid
CGA 193468	4-(5-chloro-3-fluoro-2-pyridinyloxy) phenol

Table 2 Toxicity Profile of Technical Clodinafop-propargyl

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted.)

Study Type/Animal/PMRA#	Study Results
Toxicokinetic Studies	
Single Dose (Gavage) Specific pathogene free (SPF) Rats PMRA#: NA	Single gavage dose administration of 25 mg/kg bw of [U-^{14}C]phenyl or [2-^{14}C]pyridinil clodinafop-propargyl (CGA 184927) (5♂/group) Distribution: [U-^{14}C]phenyl CGA 184927: Residues in fat, liver, kidney and carcass were 3.8%, 0.8%, 0.2%, and 20.3% of the AD, respectively. Total recovered radioactivity was 95.8% of the AD. [2-^{14}C]pyridinil CGA 184927: Residues in fat, liver, kidney and carcass were 3.9%, 0.9%, 0.2% and 17.9% of the AD. Total recovered radioactivity was 97.6% of the AD. Metabolism: Urine: The major metabolite was (R)-2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)-phenoxy]propionic acid = CGA 193469 accounting for 36.7% to 39.1% of the AD. In addition, seven unidentified metabolites were isolated, ranging from 0.1% to 5.2% of the AD. Unchanged parent

Study Type/Animal/PMRA#	**Study Results**
	compound was not identified. Feces: The major metabolite extracted in the urine was CGA 193469 which accounted for 15.7% to 16.9% of the AD. Six unidentified metabolites were isolated, ranging from 0.3% to 1.4% of the AD. Fat: All metabolites were acylglycerides. The majority of which were hybrid di-and triacylglycerides accounting for about 3.5% to 17.0% of the AD, respectively. Liver, kidney and carcass: similar to excreta and fat. Excretion: [U-^{14}C]phenyl CGA 184927: in feces (11.2%) and in urine (15.4%) after 24 hrs. In feces (22.3%) and in urine (48.4%) 7 days after dosing. [2-^{14}C]pyridinil CGA 184927: in feces (13.3%) and in urine (14.8%) after 24 hrs. In feces (23.6%) and in urine (51.1%) after 7 days.
Single Dose (Gavage) SPF Rats PMRA#: NA	Single gavage dose administration of 149, 154 169, and 185 mg/kg bw of [2-^{14}C]pyridinil CGA 184927 in experiment a and b. (5♂/group). Experiment a: peanut oil/acetone. Experiment b: hydroxpropylmethylcellulose. Plasma: Experiment a) Mean maximum plasma concentration (C_{max}) of radioactivity was 467.9 µg/g @ 4 hrs post-dosing. By 48 hrs, mean concentration was = 3.6 µg/g. Based on first order kinetics, $T_{1/2}$ = 6.2 hrs, AUC = 9906 µg/g × hr Experiment b) C_{max} = 299 µg/g @ 2 hrs post-dosing. Concentration was 2.1 µg/g @ 48 hrs post-dosing. Based on first order kinetics, $T_{1/2}$ = 6.3 hrs, AUC = 3018 µg/g × hr Peanut oil suspension had higher C_{max} at a delayed T_{max}, resulting in a 3.3 times higher AUC value indicating that the absorption of the test material is 3 times higher when administered in peanut oil. Whole blood: Experiment a) C_{max} = 308 µg/g @ 4 hrs post-dosing. C_{max} = 2.9 µg/g @ 48 hrs post-dosing. Based on first order kinetics, $T_{1/2}$ = 6.5 hrs, AUC = 6307 µg/g × hr Experiment b) C_{max} = 182 µg/g @ 2 hrs post-dosing. C_{max} = 1.9 µg/g @ 48

Study Type/Animal/PMRA#	Study Results
	hrs post-dosing. Based on first order kinetics, $T_{1/2}$ = 6.8 hrs, AUC = 1945 µg/g × hr Excretion: Experiment a) urine: 14.5% (8 hrs), 85.1% (4 days), feces: 11.9% (4 days) Experiment b) urine: 33.2% (8 hrs), 73.1% (4 days), feces: 12.8% (4 days)
Single Dose/repeated dose (Gavage) SPF rats PMRA#: NA	Single gavage dose administration of 0.5 or 50 mg/kg bw of [U-^{14}C]phenyl clodinafop-propargyl or single gavage dose 0.5 mg/kg bw/day [U-^{14}C]phenyl or 2-^{14}C]pyridinil clodinafop-propargyl after 14 daily doses of unlabeled test material. Absorption and Distribution: **0.5 mg/kg bw**: ♂: Residues were highest in fat, kidneys, liver and bone marrow. Carcass and tissues contained 30.9% of the AD. ♀: Residues were highest in fat, ovaries, uterus and kidneys. Carcass and tissues contained 2.4% of the AD. **0.5 mg/kg bw (after 14 daily doses)**: ♂: Residues were highest in fat, bone marrow, kidneys and liver. Carcass and tissues contained 13.8% of the AD. ♀: Residues were highest in bone marrow, fat, kidneys and thymus. Carcass and tissues contained 1.5% of the AD. **50 mg/kg bw**: ♂: Residues were highest in fat, liver, bone marrow, and kidneys. Carcass and tissues accounted for 31% of the AD. ♀: Residues were highest in fat, uterus, bone marrow, and ovaries. Carcass and tissues contained 5.4% of the AD. Less than 0.1% of the AD was detected in volatiles or in expired air. Metabolism: Urine: CGA193469 accounting for 27% to 38% (♂, all dose levels) and 78% to 85% (♀, *all* dose levels). CGA 214111 accounting for 0.2 to 0.9% of the AD for all groups A high percent of polar fractions was also seen in male rats. Six unidentified

Study Type/Animal/PMRA#	**Study Results**
	metabolites were isolated, ranging from 0.2% to 4.1% of the AD. Unchanged CGA184927 was not detected in the urine. Feces: CGA 193469 accounting for 9.2% to 10.3 of the AD for males and 0.8% to 2.8% of the AD in females in all groups. (Sex, dosing regime and dose level did not produce different fecal metabolic profile.) Eleven minor metabolites were also isolated ranging from 0.1% to 3.0% of the AD. Three were identified as: a) CGA214111 = 0.1 to 0.4% of the AD, b) CGA 193468 = 0.1 to 0.2% of the AD, c) unchanged CGA < 0.1 to 0.2% of the AD. Blood: only CGA 193469 was identified. Lungs: CGA 193469 and triacylglycerides were identified. **50 mg/kg bw**: ↑ liver wt Excretion: **0.5 mg/kg bw**: Urine (♂: 37%, ♀:82%) and feces (♂:15 %, ♀: 2%) 3 days post-dosing. Urine (♂: 47%, ♀:88%) and feces (♂: 20%, ♀: 2.5%) 7 days post-dosing **0.5 mg/kg bw (after 14 daily doses)**: Urine (♂: 56 %, ♀:87%) and feces (♂:16 %, ♀: 1.7%) 3 days post-dosing. Urine (♂:65 %, ♀: 92%) and feces (♂: 20%, ♀: 2%) 7 days post-dosing **50 mg/kg bw**: Urine (♂: 33%, ♀:77%) and feces (♂:16 %, ♀: 4.7%) 3 days post-dosing. Urine (♂: 44%, ♀: 89%) and feces (♂: 21%, ♀: 5.9%) 7 days post-dosing
90-Day (Diet) Determination of residues in Abdominal Fat SPF Albino Rat PMRA# 1128917 1169366	**≥ 8.2 mg/kg bw/day:** dose-related ↑ residues in abdominal fat samples (@ 14 or 18 wk, ♂ > ♀). Residues were determined at the end of a 14 week treatment period, and after a 4 week recovery period (after 18 week) in a separate group. Results demonstrated that a plateau of the residues was reached and evidence for accumulation was not observed.
12-, or 24-month	**≥ 0.031/0.034 mg/kg bw/day:** dose-related ↑ residues abdominal fat samples

Study Type/Animal/PMRA#	**Study Results**
Oral (Diet) – Determination of Residues as CGA 193469 in abdominal fat SPF Albino Rat PMRA# 1128921	(12 or 24-month, ♂>♀) Results demonstrated that a plateau of the residues was reached and evidence for accumulation was not observed.
Acute Toxicity Studies	
Acute Oral Toxicity (Gavage) SPF Albino Mice PMRA# 1128883	LD_{50} > 2000 mg/kg bw **@ 2000 mg/kg bw**: ↑ piloerection, hunched posture and dyspnea in all animals 1hr post-dosing. Recovery noted within 3 and 8 days for ♂ and ♀ respectively. One ♀ died on day 6 post-dosing. **Low acute toxicity**
Acute Oral Toxicity (Gavage) SPF hybrid Rats PMRA# 1169346	LD_{50} = 1392 mg/kg bw (♂) LD_{50} = 2271 mg/kg bw (♀) LD_{50} = 1829 mg/kg bw (♂+♀) **≥ 500 mg/kg bw**: dyspnea, curved body position, exophthalmos, and ruffled fur in all treated animals, ↓ BW **≥ 2000 mg/kg bw**: sedation Recovery noted between days 12 and 14 days Deaths: 0/10, 5/10, and 10/10 @ 500, 2000, and 5000 mg/kg bw, respectively **Slightly acutely toxic**
Acute Dermal Toxicity SPF hybrid Rats	LD_{50} > 2000 mg/kg bw **2000 mg/kg bw**: slight sedation and dyspnea as well as abnormal body posture was observed on the day of dosing. Abnormal body posture and slight dyspnea were noted up to days 2 and 7 post-exposure respectively. Ruffled fur was noted on animals from days 1–9 post-dosing. All animals

Study Type/Animal/PMRA#	**Study Results**
PMRA# 1169347	recovered by day 9. **Low acute toxicity**
Acute Inhalation Toxicity-Nose only SPF hybrid Rats PMRA# 1169348	$LC_{50} > 2.325$ mg/L 2.325 mg/L: one female died immediately after exposure. This death was considered treatment-related. Sedation, dyspnea, curved body position, and ruffled fur was noted in both control and treated animals but persisted for 1–2 additional days in the treated group. All other animals recovered by day 5. **Low acute toxicity**
Primary Eye Irritation New Zealand White Rabbits PMRA# 1169349	Corneal opacity, conjunctivae redness, chemosis and iritis were noted to variant degrees in the treated eyes. All animals recovered after 7 days. 24–72 h MAS of 3.6/110, a positive score on day 3 and negative readings on day 7 **Non-irritating**
Primary Skin Irritation New Zealand White Rabbits PMRA# 1169350	Only very slight erythema was noted in all three animals 1 hour following exposure. All animals recovered by 24 hours. **Non-irritating**
Dermal Sensitization Pirbright White Strain guinea pig PMRA#1169351	Very slight to well-defined erythema was seen in all animals 24 and 48 hours after dermal exposure. Very slight edema in 1/10 ♂ and 2/10 ♀ after 24 hours and in 2/10 ♂ and 2/10 ♀ after 48 hours. No reaction was observed in control animals. **Positive skin sensitizer**

Study Type/Animal/PMRA#	**Study Results**
Short-Term Toxicity Studies	
28-Day Oral Toxicity (Gavage) Non-guideline Tif: RAIf (SPF) albino Rat PMRA# 1239446	**Supplemental** **≥ 5 mg/kg bw/day:** ↑ blood glucose, ↑ liver wt; ↑ ALP, ↓ blood urea, ↑ hepatocyte hypertrophy (♂) **≥ 40 mg/kg bw/day:** ↓ thymus wt; ↓ BW, ↓ BWG, ↓ FC (♂); ↓ gonads wt, ↑ hepatocyte hypertrophy (♀) **200 mg/kg bw/day:** ↑ mortality, ↑ clinical signs of toxicity (apathia, ruffled fur, hunched posture, altered locomotion, ptosis, muscular weakness and salivation), ↑ liver necrosis, ↑ thymic atrophy; ↑ water consumption, ↑ hypocellularity in the bone marrow, ↑ atrophy in splenic white pulp, ↑ hyperkeratosis and parakeratosis in the non-glandular stomach ↑ caecum dilatation (♂); ↓ BW, ↓ BWG, ↓ FC, ↑ platelets, ↑ ALT, ↑ ALP, ↑ AST (♀)
28-Day Oral Toxicity (Diet) Wistar Rat Non-guideline PMRA# 1451479	**Supplemental** **≥ 25 mg/kg bw/day:** ↓ eosinophils, ↑ plasma albumin, ↑ plasma total bilirubin, ↑ ALP, ↓ ALT, ↑ liver wt, ↑ reduced glycogen in the liver, ↑ increased eosinophilia/decreased basophilia stippling (centrilobular) in the liver); ↓ BW, ↓ neutrophils, ↑ monocytes (♂) **75 mg/kg bw/day:** ↑ mortality, ↓ BW, ↑ apoptosis in the liver, ↑ mitosis in the liver, ↑ centrilobular inflammatory cell infiltration (minimal) (♂); ↓ FC(♀)
90-Day Oral Toxicity (Diet) Tif: RAIf (SPF) Albino Rat PMRA# 1239447	NOAEL = 8.2 mg/kg bw/day No treatment-related findings were observed in mortality data, clinical signs of toxicity, ophthalmological examination, and food consumption. The study included a four week recovery period, which showed some effects were reversible. **≥ 0.13 mg/kg bw/day:** ↓ eosinophils, ↓ adrenals wt (♂) *(non-adverse)* **≥ 0.92/94 mg/kg bw/day:** ↓ testes wt *(non-adverse)* **≥ 8.2 mg/kg bw/day:** ↓ Hgb; ↓ globulin, ↓ RBC, ↓ Hct, ↓ monocytes, ↑ total bilirubin, ↑ ALP, ↑ liver wt (♂); ↑ WBC, ↑ cholesterol, ↑ ovaries wt (♀) **70/71 mg/kg bw/day:** ↑ hepatocyte hypertrophy, ↑ liver necrosis; ↑ glucose, ↑ albumin; ↓ BW, ↓ BWG, ↓ water consumption, ↑ anisocytosis score, ↑ hypochromasia, ↓ cholesterol, ↓ thymus wt, ↓ spleen wt, ↑ thymus atrophy, ↑

Study Type/Animal/PMRA#	Study Results
	testes atrophy (♂); ↑ creatine, ↑ ALP, ↓ ALT, ↑ liver wt, ↓ adrenals wt (♀)
28-Day Dermal Toxicity Study Albino Rat PMRA# 1239452	NOAEL (systemic) = 50 mg/kg bw/day (♂) NOAEL (systemic) = 200 mg/kg bw/day (♀) NOAEL (irritation) ≥ 1000 mg/kg bw/day **≥ 50 mg/kg bw/day:** ↑ piloerection; ↑ liver wt, ↑ AST (♂); ↓ ovaries wt, ↓ spleen wt (♀) *(non-adverse at this dose-level)* **≥ 200 mg/kg bw/day:** ↑ ALP; ↑ hunched posture, ↓ BW, ↓ thymus wt (♂) **000 mg/kg bw/day:** ↓ FC, ↑ hepatocyte hypertrophy, ↑ thymic atrophy (♂); ↑ clinical signs of toxicity (hunched posture, dyspnea, and exophthalmos); ↓ BW, ↓ thymus wt (♀)
90-Day Oral Toxicity (Diet) Beagle Dog PMRA# 1239450	NOAEL = 0.35 mg/kg bw/day (♂) NOAEL = 1.89 mg/kg bw/day (♀) **≥ 0.35/0.39 mg/kg bw/day:** ↑ ALT, ↑ IgA in blood, ↑ creatine kinase (equivocal, pretest data too variable – males and females) *(non-adverse)* **≥ 1.73/1.89 mg/kg bw/day:** ↓ cholesterol; ↑ skin lesions (pustules in the inguinal area of 2 male dogs from days 7 to 18 and 37 to 43, respectively @ this dose and pustules in the inguinal area and on the abdomen of 2 males in the high dose from days 7 to 18), ↑ AST (♂) **7.91/7.16 mg/kg bw/day:** ↑ ALP; ↓ RBC, ↓ Hgb, ↓ Hct (♂); ↑ skin lesions (pustules in the inguinal area and on the abdomen of 1 female in the high dose from days 7 to 18), ↑ ALT (♀) ***[0.04*/34.1**/16.1***]/[0.04*/32.3**/16.9***] mg/kg bw/day:** ↑ skin lesions [in all animals of both sexes from day 63 to necropsy: Erythema (conjunctiva, ears, flews, mandible, flank, forelegs and hindlegs), pustule formation (inguinal, abdominal), purulent spots (ears, axilla), alopecia (muzzle, ears, limbs, flanks), encrustation (muzzle, ears)], ↑ tremors and decreased activity (in 3 males and 2 females during 1000 ppm dose period), ↑ diarrhea, ↓ BW, ↓ FC, ↑ incidence and severity of conjunctivitis in the eyes, ↑ ALP, ↑ vacuolated cell foci in the zona fasciculata of the adrenal cortex (all animals in this dose); One mortality, ↓ RBC, ↓ Hgb, ↓ Hct, ↑ platelets, ↓ cholesterol, ↑ AST, ↑ ALT, ↑ IgA in blood, ↑ liver wt, ↑ kidneys wt, ↑ thyroid wt (♂); ↑ ALT, AST (♀)

Study Type/Animal/PMRA#	**Study Results**
	[a]An additional dose group was also included which consisted of the following dosing period: 1-54/55 days* 66/67 days** 90 days***
12-month Oral Toxicity (Diet) Beagle Dog PMRA# 1239451 1156319	NOAEL = 3.38/3.37 mg/kg bw/day (♂/♀) **≥ 0.32 mg/kg bw/day:** ↓ blood iron conc. (♂) *(non-adverse)* **15.2/16.7 mg/kg bw/day:** ↑ clinical signs of toxicity (3/4 ♂ and 4/4 ♀: pustules, crusts, scales, erythema, alopecia, poor coat condition, redden sclera and ocular exudate – lesions were noted intermittently at various times throughout the treatment period; two ♀ withdrawn from treatment due to excessive clinical signs of toxicity: loss of body weight, decreased food consumption, paddling movements, decreased activity, abnormal gait or uncoordinated movements, dry nose, pallor, dyspnea and squealing, diarrhea (both females), and swollen and nodular paws, ↓ BWG, ↑ slight to marked anemia (1♂, 2♀ from hematology analysis: > 10% reduction in RBC parameters), ↑ incidence of chronic, moderate to severe non-specific inflammatory change in the skin (grossly described as red and thickened skin and/or scab formation in 1 ♂ and two ♀), ↑ slight hepatic parenchymal hypertrophy (one ♂ and one ♀); ↓ testes wt (♂); ↓ BW, ↓ total lipids in blood, ↓ cholesterol, ↓ total protein in blood (♀)
Chronic Toxicity/Oncogenicity Studies	
18-Month Oral Toxicity (Diet) Albino Mouse PMRA# 1123424 1123353 1158474	NOAEL = 1.10 mg/kg bw/day (♂) NOAEL = 1.25 mg/kg bw/day (♀) **≥ 0.113/0.129 mg/kg bw/day:** ↑ ALP, ↑ AST (♀) *(non-adverse at this dose-level)* **≥ 1.10/1.25 mg/kg bw/day:** ↑ ALP, ↑ hepatocyte hypertrophy (♂); ↑ Kupffer cells, pigmentation (♀) *(non-adverse at this dose-level)* **≥ 11.0/12.6 mg/kg bw/day:** ↑ liver wt, ↑ intrahepatic bile duct hyperplasia; ↑ ALT, ↑ AST, ↑ Kupffer cells pigmentation in the liver, ↑ hepatocyte pigmentation, ↑ hepatocytes necrosis, ↑ foci of cellular change (basophilic) in the liver (♂); ↑ hepatocyte hypertrophy, ↑ lymphohistiocytic infiltration in the liver (♀)

Study Type/Animal/PMRA#	Study Results
	29.6/33.1 mg/kg bw/day: , ↑ thymic atrophy; ↑ hepatocellular adenomas, ↑ combined hepatocellular adenomas and carcinomas, ↑ mortality, ↓ BW, ↓ BWG, ↑ ALT, ↑ AST, ↑ lymphohistiocytic infiltration, ↑ hepatocellular carcinoma, ↑ incidence of small testes, ↓ testes wt, ↑ testicular tubular atrophy, ↓ spermatogenesis (♂); ↑ hepatocyte pigmentation, ↑ recent necrosis in the liver, ↑ hemangioma, ↑ angiosarcoma, ↑ vascular tumours (♀) **Evidence of oncogenicity** Liver tumour incidences in ♂: Adenomas: 7/60, 9/60, 9/60, 11/60, 30/60 Carcinomas: 2/60, 4/60, 2/60, 4/60, 8/60 Combined (adenomas and carcinomas): 9/60, 13/60, 11/60, 15/60, 38**/60 * statistically significant at $p < 0.01$(trend and pairwise) Vascular tumour incidences in ♀: Hemangiomas: 0/60, 1/60, 0/60, 1/60, 2/60 Angiosarcomas: 0/60, 1/60, 0/60, 1/60, 3/60 Combined (hemangiomas and angiosarcomas): 0/60, 2/60, 0/60, 2/60, 5*/60 * statistically significant (trend at $p<0.01$ and pairwise at $p<0.05$)
24-Month Oral Toxicity (Diet) Albino rats PMRA# 1451480 1451482 1451483 1128894	NOAEL = 0.32 mg/kg bw/day (♂) NOAEL = 0.37 mg/kg bw/day (♀) **≥ 0.32/0.37 mg/kg bw/day:** ↓ testes wt, ↑ hepatocyte hypertrophy (♂)*(non-adverse)* **≥ 10.2/11.3 mg/kg bw/day:** ↑ AST, ↑ liver wt, ↑ recent necrosis in the liver, ↑ tubular pigmentation in the kidneys, ↑ CPN; ↓ RBC, ↓ Hgb, ↓ Hct, ↑ ALP, ↑ ALT, ↑ kidneys wt, ↑ fibrosis of the liver parenchyma and capsule, ↑ nodular and focal hyperplasia of the liver, ↑ recent and hepatocyte necrosis (♂); ↑ cholesterol, ↑ phospholipids, ↑ hepatocyte hypertrophy, ↑ hypertrophy of follicular epithelium of the thyroid (♀) **26.3/29.5 mg/kg bw/day:** ↓ BW, ↓ BWG, ↑ alveolar foam cells; ↑ prostate adenoma, ↑ combined prostate adenoma and carcinoma (♂); ↑ ALP, ↑ triglycerides, ↑ kidneys wt, ↑ ovaries wt, ↑ fibrosis of the liver parenchyma

Study Type/Animal/PMRA#	**Study Results**
	and capsule, ↑ nodular and focal hyperplasia of the liver, ↑ recent and hepatocyte necrosis, ↑ hyperplasia of granulosa-theca cell in the ovaries (PWG re-read), ↑ ovarian tubular adenomas (original study pathologists evaluation only) (♀) **Evidence of oncogenicity** Prostate tumour incidences (PWG re-read): Adenomas: 8/80, 10/80, 8/80, 11/80, 16/80 Carcinomas: 0/80, 0/60, 2/80, 2/60, 2/80 Combined (adenomas and carcinomas): 8/80, 10/80, 10/80, 13/60, 18*/60 * statistically significant (trend at $p<0.01$ and pairwise at $p<0.05$) Ovarian tumour incidences: Tubular adenomas: 2/80, 1/80, 1/80, 1/80, 9*/80 Tubular carcinomas: 0/80, 0/80, 0/80, 0/80, 0/80 * statistically significant (trend at $p<0.01$ and pairwise at $p<0.05$)
Developmental/Reproductive Toxicity Studies	
Two-Generation Reproduction Toxicity (Diet) Sprague-Dawley (SD) Rat PMRA# 1239131 1128906	**Parental Toxicity** NOAEL = 3.21 mg/kg bw/day (♂) NOAEL = 3.77 mg/kg bw/day (♀) **≥ 0.33/0.41 mg/kg bw/day:** ↑ liver wt (F_1♂); ↓ FC (P♀ during lactation period) (*non-adverse*) **≥ 31.7/37.5 mg/kg bw/day:** ↑ liver wt (in P♂, P♀, and F_1♀), ↑ dilatation of renal pelvis; ↓ BW, ↓ BWG, ↓ FC (P♂, and F_1♂); ↓ FC (F_1♀: during the lactation period) **64.2/73.6 mg/kg bw/day:** ↑ kidneys wt, ↑ hepatocyte hypertrophy, ↑ kidneys lesions (focal subacute to chronic interstitial nephritis, and pyelonephritis, focal proliferation of tubular epithelium, hyaline casts, parenchymal atrophy, pigment deposits in tubules, loss of tubular epithelium with gray masses in tubular lamina, and pelvis and tubular dilatation); ↑ mortality, ↓ testes wt, ↓

Study Type/Animal/PMRA#	Study Results
	epididymides wt (P generation only) **Offspring toxicity** NOAEL = 0.41 mg/kg bw/day (♀) **≥ 3.77 mg/kg bw/day:** ↓ pup BW (F_1), ↓ litter BW (F_1), ↓ pup BWG (F_1), ↑ unilateral/bilateral dilatation of the renal pelvis (F_2) **≥ 37.5 mg/kg bw/day:** ↓ BW (F_2), ↓ viability index (F_1 only), ↓ weaning index (F_1 only), ↑ unilateral/bilateral dilatation of the renal pelvis (F_1), ↓ # of pup born alive (F_2 only) **Reproductive toxicity** NOAEL = 31.7/37.5 mg/kg bw/day (♂/♀) **≥ 64.2/73.6 mg/kg bw/day:** ↑ number of females with no pups delivered (F_1), ↓ gestation index (F_1) Sperm parameters (motility and morphology), estrous cycle length and periodicity, and ovarian follicle were not examined **Sensitivity of the young**
Prenatal Developmental (Gavage) Range-Finding SD Rat PMRA# 1158416	**Supplemental** **Maternal Toxicity** **≥ 80 mg/kg bw/day:** ↓ FC **160 mg/kg bw/day:** ↓ BW, ↓ BWG, ↑ resorptions **Developmental Toxicity** **≥ 40 mg/kg bw/day:** ↓ live fetuses **≥ 80 mg/kg bw/day:** ↓ fetal BW, ↓ litter BW,
Prenatal Developmental (Gavage) SD Rat	**Maternal Toxicity** NOAEL = 40 mg/kg bw/day **160 mg/kg bw/day:** ↓ BW, ↓ FC, one animal had early resorption and no

Study Type/Animal/PMRA#	**Study Results**
PMRA# 1158475 1239120 1128906	live fetuses on GD20 **Developmental Toxicity** NOAEL = ND LOAEL = 5 mg/kg bw/day **≥ 5 mg/kg bw/day:** ↑ incomplete ossification (13th vertebral centrum), ↑ bilateral torsion and distension of the ureters, ↑ absent ossification (sternebra 6) **≥ 40 mg/kg bw/day:** ↓ litter BW, ↑ hematoma in the head, ↑ incomplete ossification (vertebral centra 10 and 12; cranial bones [parietals, interparietals, occipitals, and squamosal], and right and left metacarpals) **≥ 160 mg/kg bw/day:** ↓ fetal BW, ↑ incomplete ossification (vertebral centrum 11; sternebrae 2, 3, 4, and 6), ↑ absent ossification (sternebra 5; and caudal vertebral arches 1 and 2) **Sensitivity of the young; no evidence of malformations**
Prenatal Developmental (Gavage) Hybrid albino (HyCr) Rabbit PMRA# 1158417 1239109	**Maternal Toxicity** NOAEL = 5 mg/kg bw/day LOAEL = 25 mg/kg bw/day No treatment-related effects on gravid uterine wt, post-implantation loss, # of live and dead fetuses/litter. **≥ 25 mg/kg bw/day:** One ♀ was sacrificed in a moribund condition on GD 22 with clinical signs of toxicity (nasal discharge, marked salivation, ataxia, and severe tremors (particularly of the head) and were first noted on GD 16/17; gross post mortem did not reveal any significant findings) **≥ 125 mg/kg bw/day:** ↑ mortality (5/18 [GD 14-22], 11/14 [GD 11-15] @ 125, and 175 mg/kg bw/day, respectively), ↑ clinical signs of toxicity (laboured breathing, reduced activity, tremors, marked salivation, ataxia, pallor, and nasal discharge) started on Day 2 of dosing, ↓ BW (in dying animals) **175 mg/kg bw/day:** One doe aborted on GD 23

Study Type/Animal/PMRA#	**Study Results**
	Developmental toxicity NOAEL ≥ 125 mg/kg bw/day LOAEL = ND No treatment-related effects on fetal body weight, external, visceral and skeletal examination were noted. Due to high mortality @ 175 mg/kg bw/day, the fetal data for this group was excluded from analyses (only one litter was produced) **No evidence of malformations or sensitivity of the young**
Genotoxicity Studies	
In vitro bacterial gene mutation assay (Salmonella Typhimurium) Strains TA 98, TA100, TA1535 and TA1537 PMRA# 1239140 2349849	**Negative** Precipitation was noted starting at 313 µg/0.1 mL.
In vitro DNA repair/ unscheduled DNA synthesis Tif: RAIf (SPF) Rat hepatocytes PMRA# 1239141	**Negative** Compound precipitation was noted at levels ≥ 4000 µg/mL. Cytotoxicity was noted in the preliminary cytotoxicity test at 94.8 µg/mL. The positive control induced the expected marked increased in unscheduled DNA synthesis .
In vivo clastogenicity/Mi	**Negative**

Study Type/Animal/PMRA#	**Study Results**
cronucleus Assay SPF Naval Medical Research Institute -derived mice bone marrow cells PMRA# 1239142 2349851	A slight but statistically significant increase in MnPCE frequencies was noted at 1667 and 5000 mg/kg bw for the 24 hour sampling group for both ♂ and ♀ (0.12 and 0.02% at 1667 mg/kg bw and 0.08 and 0.02 at 5000 mg/kg bw). This increase was considered to be due to unusually low control values (0% for both sexes), when compared to historical control data (0.06±0.05 in ♂ and 0.05±0.03 in ♀).
In vivo/In vitro Unscheduled DNA synthesis in Rat Hepatocytes (gavage) Wistar Rats PMRA# 1451487	**Negative** ≥ 1000 mg/kg bw: Reduced locomotor activity 2000 mg/kg bw: curved body position
In vitro mammalian cell Mutagenicity assay Chinese Hamster lung V79 Cells PMRA# 1239143	**Negative** The rationale for lower doses in the presence of metabolic activation was that cytotoxicity was observed around 150 µg/mL.
In vitro mammalian cell Mutagenicity assay Chinese Hamster Ovary Cells PMRA#	**Negative** Cytotoxicity noted starting at 1000 µg/mL ≥ 125 µg/mL: A slight (not statistically significant) increase (2.0 to 6.5% for -S9, 1.5 to 4.5% for +S9) in mean chromosomal aberrations was noted (control mean: -S9 2.5% to 3.5%, +S9: 2.0%)

Study Type/Animal/PMRA#	**Study Results**
2345277	
In vitro mammalian cell Mutagenicity assay Chinese Hamster Ovary Cells PMRA# 1451484	**Negative** Positive (+S9) at cytotoxic doses only Precipitation was noted at 100 µg/mL and above The study was negative up to adequate cytotoxic concentrations (50–100 µg/mL) in the non-activated phase of testing. However, in three of four assays, statistically significantly increase in clastogenicity (↑ 10–30% specific chromosomal aberrations and polyploid metaphases) was seen at 50 in the presence of S9 activation. The effect was confined to this concentration and occurred only under cytotoxic concentrations (45 to 79% decreases in mitotic index accompanied by 70% reduction in cloning efficiency). Clastogenic response was likely due to cytotoxicity.
In vitro mammalian cell cytogenetics/ clastogenicity assay Human lymphocytes PMRA# 1239144	**Inconclusive** Cytotoxicity observed at 500 µg/mL (-S9) and at 62.5 µg/mL (+S9) or above Presence of rare complex chromosome aberrations (e.g. presence of metaphases with unspecific aberrations for example, chromatid gaps, iso-chromatid gaps, premature chromosome condensation, chromosome decay), and a very low percent of metaphases with specific aberration, but not dose-related. (Control group had no aberrations of any kind)
Neurotoxicity Studies	
Acute Neurotoxicity (gavage) Wistar Rats PMRA# 1451488 1451489	NOAEL = 100 mg/kg bw/day (♂) NOAEL = 1000 mg/kg bw/day (♀) No treatment-related effect on hind limb grip strength, time to tail-flick or brain weights. **≥ 300 mg/kg bw/day:** ↓ BWG, ↓ BW, ↓ FC, ↑ demyelination of proximal tibial nerve, ↓ forelimb grip strength (♂)

Study Type/Animal/PMRA#	Study Results
	1000 mg/kg bw/day: ↑ clinical signs of toxicity (hunched posture, piloerection, subdued behaviour, red/brown staining of the front limbs, redness and swelling of the paws, scabbing of the underside of the chin, and/or eye discharge, "diminished eyes", chromodacryorrhea, and salivation), ↓ motor activity, ↑ demyelination of proximal sciatic and distal tibial nerves (♂) - Environmental conditions (i.e., sound level, temperature, humidity, lighting, odors, time of day, and environmental distractions) during the functional observation battery and motor activity testing were not provided
90-Day Neurotoxicity (Diet) Wistar Rats PMRA# 1451490	NOAEL = 1.2 mg/kg bw/day (♂) NOAEL ≥ 86.3 mg/kg bw/day (♀) No treatment-related effect on clinical signs of toxicity, mortality, brain weight, gross pathology or neuropathology. **≥ 9.3/10.8 mg/kg bw/day:** ↓ BW, ↓ BWG (♂) **78.7/86.3 mg/kg bw/day:** ↓ FC; ↑ motor activity (♂); ↓ BWG (♀) - Environmental conditions (i.e., sound level, temperature, humidity, lighting, odors, time of day, and environmental distractions) during the functional observation battery and motor activity testing were not provided. - It was unclear whether motor activity included locomotor activity alone or total motor activity (locomotor and ambulatory motor activity).
Developmental Neurotoxicity (Diet) Wistar Rat PMRA# 1451492 1451493 1451507 1451504 1451506 1451503	**Maternal toxicity** NOAEL = 9.0 mg/kg bw/day No treatment-related effects on mortality, clinical signs of toxicity, FOB, reproductive performance and post-mortem examination. **44.0/85.5 mg/kg bw/day:** ↓ BW, ↓ BWG, ↓ FC **Developmental toxicity** NOAEL = 9 mg/kg bw/day **≥ 9.0/18.0 mg/kg bw/day:** ↓ BW; delayed preputial separation (♂) (*non-adverse*)

Study Type/Animal/PMRA#	Study Results
	44.0/85.5 mg/kg bw/day: ↑ liver wt; ↓ auditory startle reflex (PND 23) in peak amplitude, ↓ piriform cortex thickness (9% on PND 63) (♂); ↓ hippocampus length (8%), ↓ hippocampus width at the dentate gyrus (6%) ↓ corpus callosum thickness (8%) on PND 12, ↑ corpus callosum thickness (24% on PND 63), delayed vaginal opening (♀) **Sensitivity of the young** Motor activity assessment was determined to be inadequate because of the lack of habituation in the female control groups on PND 60 confounded the interpretation of the effects seen in the treated groups (it is unclear if the lack of habituation observed in treated groups is treatment-related). Brain morphometry was examined in this study in control and high dose animals. Additional brain morphometry analysis was performed on animals from the low and mid-dose groups in a follow up study. Due to a number of confounding variables including, the number (over 4 years) of years between the original and supplemental study, the lack of a clear dose-response relationship and the change in study pathologists between the original and supplemental study, the supplemental brain morphometry analysis was considered of limited utility and was not considered in the toxicological assessment. Y maze performance was assessed, no treatment-related effects were observed. All groups demonstrated the capacity to reduce the length of trials and learning of the task on both PND 24 and 62. However, as demonstrated by the positive control study, due to the lack of complexity of this maze design, subtle treatment-related effects on learning and memory were not well distinguished using this testing procedure.
Developmental Neurotoxicity (Diet) Wistar Rat Range-Finding	**Supplemental** **Maternal Toxicity** No treatment-related effects on clinical signs of toxicity **≥ 41.9/82.5 mg/kg bw/day:** ↓ FC, ↑ liver wt **≥ 78.1/146 mg/kg bw/day:** ↓ BW **118/202 mg/kg bw/day:** ↑ whole litter loss (2/10 vs. 0/10 in controls)

Study Type/Animal/PMRA#	Study Results
PMRA# 1451491	**Developmental Toxicity** **≥ 41.9/82.5 mg/kg bw/day:** ↓ pup BW, ↓ total litter wt, ↑ liver wt, **118/202 mg/kg bw/day:** ↓ pup survival, ↓ litter size, ↑ "cold" pups, ↑ small pups
Special Studies (non-guideline)	
Species Differences in the Regulation of Gene Expression induced by CGA 193469 (the major metabolite of CFP) PMRA# 1451495	The study illustrated that CGA193469 can activate the rat but not the human acyl CoA oxidase (ACO) gene promoter. List of deficiencies: • Validation of the test system using a positive control for the human ACO promoter was not demonstrated. • Test material information (description, batch # and purity), • The type of culture media and the standard procedures used to prepare the cell cultures • Age, weight, strain and other relevant information of the animals that were used for isolation of the cultures • When treatment was initiated (i.e., how long before and whether a cell culture was allowed to form a viable monolayer) • Detailed description of transfection protocol and assay used for the determination of β-gal and luciferase activity • Statistical analysis (if any) used were not provided. • The study initiation and completion dates were also not explicitly stated. • Unsigned compliance certificate.
7-Day Oral (Diet) Effects on liver cell proliferation upon subchronic oral (feeding)	**≥ 0.65 mg/kg bw/day:** ↑ liver weight, ↑ proliferation (BrdU labeling) **32.5 mg/kg bw/day:** ↑ mainly diffuse, moderate to severe hepatocellular hypertrophy along with a cytoplasm of granular appearance in all animals

Study Type/Animal/PMRA#	**Study Results**
administration to Male Mice CD-1 Mice PMRA# 2346275	
14-day oral (Diet) Effect of CGA 184927 on Selected Biochemical Parameters in the Mouse Liver SPF Mice PMRA # 1451496	**≥ 3.8 mg/kg bw/day:** ↑ liver weight, ↑ induction of Cyp4a (immunoblot analysis), ↑ lauric acid 11-hydroxylase activity, ↑ lauric acid 12-hydroxlase activity, ↑ microsomal epoxide hydrolase activity, ↑ peroxisomal fatty acid β-oxidation activity,↑ formation of estriol from estradiol in vitro **≥ 17.0 mg/kg bw/day:** ↑ protein content in liver microsomal and 100xg supernatant fraction, ↓ induction of Cyp3a (immunoblot analysis), ↓ testosterone oxidation rate), ↓ glutathione S-transferase activity.
Short-term oral (Diet) Assessment of Hepatic Cell Proliferation in Male Mice Upon Treatment with CGA 184927 SPF Mice PMRA # 1451499	**≥ 3.8mg/kg bw/day:** ↑ liver weight, ↑ hepatocellular mitotic activity, ↑ hepatocellular hypertrophy, ↑ BrdU labelling **≥ 15 mg/kg bw/day:** ↑ hepatocellular mitotic activity, ↑ hepatocellular necrosis **37 mg/kg bw/day:** ↑ inflammatory cell infiltration
28-day Oral (Diet) Effect of CGA 184927 on peroxisome proliferation in the Mouse Liver	**≥ 3.8 mg/kg bw/day:** ↑ peroxiosmal volume density **37 mg/kg bw/day:** ↑ immunohistochemical detection of peroxisome catalase

Study Type/Animal/PMRA#	Study Results
SPF Mice PMRA # 1491498	
Metabolite incorporation into triacylglyceride: Species comparison PMRA#: NA	The amount of CGA 193469 incorporated into triacylglycerides after incubation in suspended hepatocytes, expressed as nmol × 10^7 viable cells were higher in rodents compared to guinea pig and monkeys: The amount incorporated was generally low for all species, ranging from 0.1% to 0.9% of the AD. Higher incorporated rate was noted in rat and mouse compared to guinea pig and monkey. Between 87.3% to 96.9% of the AD was recovered as unchanged CGA 193469
CGA193469 peroxisomal β-oxidation in rat, mouse, marmoset and guinea pig hepatocytes PMRA # 1239453	Cytotoxicity (under light microscopy): Exposure to 10 µg/mL CGA 184927 for 3 days resulted in slight to strong deterioration of the rat, mouse and guinea pig hepatocyte monolayers. Dose-related increase in intracytoplasmic or intercellular vacuoles or droplets (lipid) were observed. Rat hepatocytes were most sensitive to the cytotoxic effects of CGA 184927. This was supported by the finding that in the rat the proportion of LDH activity in the culture medium was increased at 10 µg/mL (28 µM). Propargyl alcohol was at least as toxic to rat and mouse hepatocyte as CGA 184927. In mouse hepatocyte, the proportion of LDH activity in the medium was increased at 100 µg/mL. No effect on LDH activity was noted in guinea pig hepatocyte at 10 µg/mL (28 µM) and higher concentrations were not tested. Treatment with CGA 193469 did not elicit a change in the proportion of LDH activity in the culture medium in hepatocytes from any of the test species. Peroxisomal β-oxidation (only CGA 193469 was tested): In the rat, a dose-related increase in peroxisomal β-oxidation was noted.

Study Type/Animal/PMRA#	Study Results
	In mice, a peroxisomal β-oxidation was noted was increased @ 30 µg/mL or higher. In guinea pigs, marginal increase @ 100 µg/mL. In marmoset hepatocytes, no peroxisomal oxidation was noted.
The effects of CGA 193469 (the major metabolite of CFP) on the peroxisomal enzymatic marker palmitoyl-CoA oxidase in human hepatocytes PMRA # 1128923	Cytotoxicity: No treatment-related changes in hepatocyte morphology or intracellular LDH levels after 24, 48, and 72 hour incubation. Peroxisomal β-oxidation activity: ↑ 23% compared to control @ 100 µM. Treatment with CGA 193469 or bezafibric acid, at all concentration tested, was not cytotoxic to human hepatocytes, in vitro. Under the condition of this study, neither CGA 193469 nor bezafibric acid induced peroxisomal β-oxidation in human hepatocytes in vitro. However, in the absence of a known concurrent human positive control to validate the test system, i.e., a substance known to elicit peroxisomal β-oxidation in human hepatocytes, this cannot be definitely concluded.
90-Day Oral (Diet) Effect of CGA 184927 on Selected Biochemical Parameters in the Rat Liver SPF Albino Rat PMRA#: NA	**≥ 0.13 mg/kg bw/day:** ↑ cytochrome P-450, ↑ styrene oxide hydrolase, ↑ induction in cytochrome P-452 (immunoblot analysis) (♂) **≥ 0. 92/0.94 mg/kg bw/day:** ↑ ethoxycoumarin O-deethylase, ↑ fatty acyl-CoA β-oxidation (♂) **≥ 8.2 mg/kg bw/day:** ↑ cytochrome P-450, ↑ ethoxycoumarin O-deethylase, ↑ fatty acyl-CoA β-oxidation (♀) **70/71 mg/kg bw/day:** ↑ microsomal and cytosolic protein, ↑ lauric acid 11-hydrolase (other doses not tested), ↑ enoyl-CoA hydratase-3-hydroxy-CoA dehydrogenase (peroxisomal bifunctional enzyme) (immunoblot analysis); ↓ glutathione S-transferase (♂); ↑ styrene oxide hydrolase, ↑ uridine 5'-diphospho-glucuronosyltransferase, ↑ induction in cytochrome P-452 (immunoblot analysis) (♀) A satellite group was maintained in control diet for assessment after 4-week recovery Recovery period: **70/71 mg/kg bw/day:** ↑ microsomal and cytosolic protein, ↑ cytochrome P-

Study Type/Animal/PMRA#	Study Results
	450, ↑ fatty acyl-CoA β-oxidation (♂) (all slightly recovered)
90-Day Oral (Diet) Electron microscopy study of liver samples SPF Albino Rat PMRA#: NA	**70/71 mg/kg bw/day:** ↑ number of matrical granules (Ca^{2+} stores) in hepatic mitochondria, in females these granules tended to aggregate into multigranular complexes; ↑ in the number and size of peroxisomes with matrical inclusion bodies in some of the enlarged peroxisomes (♂) A satellite group was maintained in control diet for assessment after 4-week recovery Recovery period: @ 18-wk, peroxisome number and size were comparable Increased incidence of matrical granules was still evident at 18 weeks, both sexes, indicating that these mitochondrial changes were not fully reversible.
90-Day Oral (Diet) Electron microscopy study of liver samples SPF Albino Rat PMRA# 1451497	**70/71 mg/kg bw/day:** ↑ peroxisomal volume density, A satellite group was maintained in control diet for assessment after 4-week recovery Recovery period: After 28 days of recovery, the mean peroxisomal volume density returned to control values.

Table 3 Toxicology Reference Values for Use in Human Health Risk Assessment for Clodinafop-propargyl

Exposure Scenario	Endpoint	Study/Point of Departure	CAF or MOE[1]
ARfD (all populations)	Decreased auditory startle reflex and changes in brain morphometrics	Developmental neurotoxicity study in rats NOAEL = 9 mg/kg bw/day	300
	ARfD (all population) = 0.03 mg/kg bw		

Exposure Scenario	**Endpoint**	**Study/Point of Departure**	**CAF or MOE[1]**
Chronic Dietary	Liver toxicity (elevated enzyme activities, increased weight and histopathological findings) and kidney toxicity (chronic progressive nephropathy, and tubular pigmentation)	24-month chronic/carcinogenicity study in rats. NOAEL = 0.3 mg/kg bw/day	100
	ADI = 0.003 mg/kg bw/day		
Short-, and Intermediate-term dermal and inhalation	Increased incidence of unilateral/bilateral dilatation of the renal pelvis in F_2 pups and decreased pup (and litter) weight during late lactation in F_1	Two-generation reproduction toxicity study in rats NOAEL: 0.41 mg/kg bw/day	100
Cancer	q_1* value = 0.0302 (mg/kg bw/day)$^{-1}$ for rat prostate adenomas and carcinomas (combined) which is also protective of vascular tumours		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments.

Appendix IV Dietary Exposure and Risk Assessments

Table 1 Dietary Chronic Exposure and Risk Assessments

Population Subgroup	Food only		Food and Drinking Water	
	Exposure (mg/kg bw/day)	%ADI[1]	Exposure (mg/kg bw/day)	%ADI[1]
General Population	0.000031	1.0	0.000062	2.1
All Infants (<1 year old)	0.000017	0.6	0.000131	4.4
Children 1–2 years old	0.000081	2.7	0.000123	4.1
Children 3–5 years old	0.000081	2.7	0.000115	3.8
Children 6–12 years old	0.000058	1.9	0.00008	2.8
Youth 13–19 years old	0.000034	1.1	0.000056	1.9
Adults 20–49 years old	0.000025	0.8	0.000055	1.8
Adults 50+ years old	0.000021	0.7	0.000050	1.7
Females 13–49 years old	0.000025	0.8	0.00005	1.8

[1] Acceptable Daily Intake (ADI) of 0.003 mg/kg bw/day.

Table 2 Dietary Acute Exposure and Risk Assessments

Population Subgroup	Food only		Food and Drinking Water	
	Exposure (mg/kg bw)	%ARfD[1]	Exposure (mg/kg bw)	%ARfD[1]
General Population	0.000092	0.31	0.000151	0.50
All Infants (<1 year old)	0.000086	0.29	0.000314	1.05

Population Subgroup	Food only		Food and Drinking Water	
	Exposure (mg/kg bw)	%ARfD[1]	Exposure (mg/kg bw)	%ARfD[1]
Children 1–2 years old	0.000190	0.63	0.000262	0.87
Children 3–5 years old	0.000176	0.59	0.000235	0.78
Children 6–12 years old	0.000134	0.45	0.000184	0.61
Youth 13–19 years old	0.000086	0.29	0.000132	0.44
Adults 20–49 years old	0.000062	0.21	0.000125	0.42
Adults 50+ years old	0.000049	0.16	0.000106	0.35
Females 13–49 years old	0.000061	0.20	0.000124	0.41

[1] Acute Reference Dose (ARfD) of 0.03 mg/kg bw.

Table 3 **Dietary Cancer Exposure and Risk Assessments**

Population Subgroup	Food only		Food and Drinking Water	
	Exposure (mg/kg bw/day)	Lifetime Risk	Exposure (mg/kg bw/day)	Lifetime Risk
General population	0.000001	3×10^{-8}	0.000031	1×10^{-6}
Potency factor (q_1*) of 0.0302 $(\text{mg/kg bw/day})^{-1}$				

Appendix IV.2 Food Residue Chemistry Summary

The nature of the residue in livestock and plant commodities is adequately understood based on metabolism studies in lactating goats, laying hens and spring wheat. The residue definition for enforcement of MRLs is the sum of clodinafop-propargyl and its acid metabolite CGA-193469. No change is proposed to this residue definition as a result of the re-evaluation.

Available enforcement analytical methods for clodinafop-propargyl and its acid metabolite CGA-193469 in plant and animal matrices are deemed adequate.

The available crop field trial data are sufficient to support the current MRL specified in Canada for wheat.

Currently, no plantback interval is specified on Canadian labels. Based on available data, residues are not expected to occur in rotational crops with a plantback interval of 30 days. Therefore, it is proposed that the Canadian label be amended to specify a plantback interval of 30 days for all non-registered crops.

As wheat commodities are livestock feed items, the current grazing restriction on most labels is 3 days. Based on available data, it is proposed that the grazing restriction be amended to specify a minimum preharvest interval of 60 days for grain and straw, 30 days for hay and 7 days for forage.

Overall, sufficient information was available to adequately assess the dietary exposure and risk from clodinafop-propargyl.

Appendix V Toxicology Endpoint Selection for Residential and Occupational Exposure

Estimated Concentrations in Drinking Water Sources: Level 1 Modelling

EECs of combined residues of the parent, clodinafop-propargyl (CGA 184927) and three breakdown products CGA 193469, CGA 193468 and CGA 302371 in potential drinking water sources (groundwater and surface water) were generated using the PWC model. For groundwater, PWC simulates leaching through a layered soil profile. The concentrations reported by PWC are average concentrations in the top 1 m of the water table. For surface water, PWC simulates pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body, a small reservoir.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 EEC estimates are expected to allow for future use expansion into other crops at the modelled application rate. Appendix V, Table 1 lists the application information and main environmental fate characteristics used in the simulations. Either nine or fourteen initial application dates between May and June were modelled. The model was run for 50 years for all cases. The largest EECs of all selected runs are reported in Appendix V, Table 2.

Table 1 Summary of Use Pattern Modelled for the Level 1 Assessment of clodinafop- propargyl

Item	Value
Crops	Wheat (spring and durum)
Method of application	Aerial, ground/foliar
Rate of application (kg a.i./ha)	0.0702
Number of applications per year	1
Typical dates of first application	May and June

Table 2 Level 1 estimated environmental concentrations of combined residues of clodinafop-propargyl in potential drinking water sources

Wheat (spring and durum), 1 × 0.0702 kg a.i./ha	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
Combined residue of Clodinafop-propargyl (CGA 184927), CGA 193469, CGA 302371 and CGA 193468	8.6	8.5	6.6	0.85

Notes:
1 90th percentile of daily average concentrations
2 90th percentile of 365-day moving average concentrations
3 90th percentile of the peak concentrations from each year
4 90th percentile of yearly average concentrations

Refinement of the Level 1 EECs was required. Level 2 EECs in drinking water were calculated using the Pesticides in Water Calculator (PWC) model. The refinements at Level 2 were calculated by selecting the highest EEC from several selected scenarios representing spring and winter wheat grown in different regions of Canada. All scenarios were run for either 50 or 100 years. Two use patterns were modelled. The existing use pattern of 70.2 g a.i./ha, for use on spring wheat in western Canada and a proposed rate of 30 g a.i./ha for use on winter wheat across Canada and on spring wheat in eastern Canada. Modelling used initial application dates between mid-May and late August based on the information provided by VRD. The Level 2 EECs of clodinafop-propargyl in potential drinking water sources from groundwater are provided in Appendix V, Table 3.

Table 3 **Level 2 Estimated Environmental Concentrations of clodinafop-propargyl in potential sources of drinking water**

Use pattern (single application)	**Groundwater (µg a.i./L)**	
	Daily[1]	**Average[2]**
Spring wheat in west Canada[3]: 70.2 g a.i./ha	0	0
Spring wheat in east Canada: 30 g a.i./ha	1.50	1.36
Winter wheat in all of Canada: 30 g a.i./ha	1.64	1.51

[1] 90th percentile of daily average concentrations

[2] The "post-breakthrough" average

[3] For British Columbia, this includes the Peace River region, the Okanagan and the Creston flats, as listed in PMRA# 2768434. EECs for coastal BC will be higher.

Details of water modelling inputs and calculations are available upon request.

Water Monitoring Data

In addition to water modelling, a search for water monitoring data on clodinafop-propargyl, in groundwater and surface water in Canada and the United States was undertaken. Monitoring data were not available for clodinafop-propargyl or CGA 193469.

The PMRA regularly communicates with the Federal, Provincial and Territorial representatives from all of the provinces and territories in Canada along with Environment and Climate Change Canada, the Department of Fisheries and Oceans and the drinking water subcommittee through Health Canada to acquire monitoring data that would be relevant to current re-evaluation programs. In Canada, only three studies monitored the occurrence of clodinafop-propargyl in Canadian waters.

Data on residues present in water samples taken in the United States are important to consider in the Canadian water assessment, therefore, American databases were searched for clodinafop-propargyl water monitoring data. Runoff events, local use patterns, site-specific hydrogeology as well as testing and reporting methods are probably more important influences on residue data rather than northern versus southern climate. As for the climate, if temperatures are cooler, residues may break down more slowly, on the other hand if temperatures are warmer, growing seasons may be longer and applications may be more numerous and frequent.

Due to the lack of water monitoring data from Canada and the United States, exposure concentrations using monitoring data could not be estimated. The concentrations of clodinafop-propargyl in surface and drinking water that was considered in the human health dietary risk assessment are the EECs determined by water modelling Level 2.

Appendix VI Commercial Mixer/Loader/Applicator Risk Assessment

Table 1 Occupational Dermal and Inhalation Exposure Risk Assessment

Crop	Formulation	Application Equipment	Max Rate (kg a.i./ha)	ATPD (ha/day)	Amount Handled per day (kg a.i./day)	Dermal Exposure[a] (mg/kg bw/day)	Inhalation Exposure[b] (mg/kg bw/day)	Dermal MOE[c]	Inhalation MOE[c]	Combined MOE[d]
Open mixer/loader (liquid - AHETF), Mid-level PPE; Open cab application, Mid-level PPE (AHETF)										
Wheat (spring, durum)	L	GB Farmer	0.0702	107	7.5	1.79E-03	2.20E-04	228	1890	204
		GB Custom	0.0702	360	25.3	6.04E-03	7.30E-04	68	562	61
		GB Custom	0.0702	215	15.1	3.6 E-03	4.40E-04	114	941	101
Closed mixer/loader (liquid – PHED), Mid-level PPE; Open cab application, Mid-level PPE (no gloves) (AHETF)										
Wheat (spring, durum)	L	GB Custom	0.0702	360	25.3	3.16E-03	5.70E-04	130	725	110
Open mixer/loader (liquid – AHETF), Mid-level PPE										
Wheat (spring, durum)	L	–	0.0702	400	28.1	4.62E-03	2.20E-04	89	1854	85
Closed mixer/loader (liquid – PHED) for aerial application, Mid-level PPE										
Wheat (spring, durum)	L	–	0.0702	400	28.1	1.42E-03	4.00E-04	289	10619	282
Open Application Aerial (PHED) Baseline PPE (no gloves)										
Wheat (spring, durum)	L	Aerial	0.0702	400	28.1	1.42E-03	2.00E-04	288	16687	283

Baseline PPE: single layer, CR gloves (only necessary for activities outside cockpit), Mid-Level PPE: coveralls over single layer, CR gloves (not necessary for closed cab application). M/L = mix/load, A = apply, ATPD = area treated per day, MOE = margin of exposure, CR = chemical resistant

Shaded cell indicates target MOE not met.

[a] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD x maximum application rate × 42% dermal absorption)/80 kg body weight

[b] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/80 kg body weight

[c] Based on a NOAEL of 0.41 mg/kg bw/day, target MOE = 100

[d] Combined MOE = NOAEL/(EXP_{derm} + EXP_{inh})

Table 2 Occupational Cancer Exposure Risk Assessment

Crop	Application Method	Rate (kg a.i./ha)	Applicator	ATPD (ha/day)	PPE/System[a]	ADD[b] (mg/kg bw/day)	LADD[c] (mg/kg bw/day)	Risk[d]
Wheat	Groundboom	0.0702	Farmer	60	Mid-level PPE, open mix/load, open cab	1.13E-03	1.58E-06	5E-08
			Custom	240	Mid-level PPE, open mix/load, open cab	4.51E-03	9.51E-05	3E-06
	Aerial		–[e]	318	Mid-level PPE, Open Mix/Load	3.85E-03	8.11E-05	2E-06
			Aerial[f]		Baseline PPE, Open Cab	1.14E-03	2.43E-05	7E-07

ATPD = Area Treated Per Day, PPE = Personal Protective Equipment, ADD = Absorbed Daily Dose, LADD = Lifetime Average Dose

[a] Personal Protective Equipment, Baseline = long pants, long-sleeved shirt and chemical resistant gloves; no gloves during application, Mid-level PPE = single layer, coveralls and chemical resistant gloves; no gloves during application

[b] Absorbed Daily Dose = daily dermal dose + daily inhalation dose, as determined by PHED/AHETF scenarios. Dermal absorption factor of 42% applied.

[c] LADD = (ADD × exposure days × working duration)/(365 days × 78 years). Treatment frequency = 1 day a year for farmers, 15 for custom applicators and 150 days for aerial mixers/loaders and applicators. Working duration = 40 years

[d] A q_1^* value of 0.0302 (mg/kg/day)$^{-1}$ was considered appropriate to use in the cancer risk assessment.

[e] Mixer/loader only

[f] Applicator only

Table 3 Post Application Risk Assessment

Crop	Activity	TCs	Rate (kg/ha)	Number of apps	Dermal MOE[a] (Target 100)	Proposed REIs (days)
Wheat (spring, durum)	Scouting	210[b]	0.0702	1	265	0.5
	Weeding	70	0.0702	1	830	0.5

TC = transfer coefficient, MOE = margin of exposure, REI = Restricted Entry Interval

[a] Dermal exposure (mg/kg bw/day) = (Dislodgeable Foliar Residue × Transfer Coefficient x Duration × Dermal Absorption x 0.001)/Body Weight

[b] Since clodinafop-propargyl is applied to wheat prior to the fourth tiller leaf stage (when the crop is very short), surrogate TCs of 210 cm^2/hr from scouting in row conditions crop cluster may be used (PMRA, 2012b)

Table 4 Cancer Exposure and Risk Estimates for Postapplication Exposure

Crop	Application Timing	Activity	Dermal Exposure[a] (mg/kg bw/day)	Exposure Days per year	ADD[b] (mg/kg bw/day)	LADD[c] (mg/kg bw/day)	Risk[d]
Wheat (spring, durum)	Post emergence	Scouting	8.11E-03	30	8.11E-03	3.42E-04	1E-05
		Scouting[e]	4.10E-03		4.10E-03	1.73E-04	5E-06
		Weeding (hand)	5.16E-04		5.16E-04	2.17E-05	7E-07

ADD = Absorbed Daily Dose, LADD = Lifetime Average Dose

[a] Dermal Exposure = (Dislodgeable Foliar Residue × Transfer Coefficient × Duration × Dermal Absorption × 0.001)/BW (kg)

[b] Absorbed Daily Dose = daily dermal dose, as determined by PHED/AHETF scenarios. Dermal absorption factor of 42% applied. Inhalation exposure was waived. See Section 4.2.2

[c] LADD = (ADD × exposure days × working duration)/(365 days × Life Expectancy). Working duration = 40 years, Life Expectancy = 78 years

[d] A q_1^* value of 0.0302 (mg/kg/day)$^{-1}$ was considered appropriate to use in the cancer risk assessment.

[e] Since clodinafop-propargyl is applied to wheat prior to the fourth tiller leaf stage (when the crop is very short), surrogate TCs of 210 cm^2/hr from scouting in row conditions crop cluster may be used (PMRA, 2013).

Appendix VII Tables and Figures

Table 1 Fate and Behaviour of clodinafop-propargyl (CGA 184927) and CGA 193469 in the Environment.

Property	Test substance	Value[1]	Transformation products	Comments	Reference
Abiotic transformation					
Hydrolysis	CGA 184927	20°C pH 1, DT$_{50}$: 5.4 d pH 5, DT$_{50}$: 184 d pH 7, DT$_{50}$: 2.7 d pH 9, DT$_{50}$: 0.1 d 22°C pH 1, DT$_{50}$: 4.5 d pH 5, DT$_{50}$: 145 d pH 7, DT$_{50}$: 2.2 d pH 9, DT$_{50}$: 0.08 d	Major: CGA 193469: 91.2% AR	Hydrolysis is a major route of dissipation for CGA 184927, especially at alkaline pH.	1128907
		pH Temp(°C) DT$_{50}$ (d) 1.2 37 1.6 4 15 7.6 **4 25 17.9** 4 40 7.1 5 15 51.3 **5 25 26.8** 5 40 12.3 7 15 12.9 **7 25 4.8** 7 40 1.2	Major: CGA 193469: 99.3% AR	Hydrolysis occurs slowly under acidic conditions but very rapidly under highly alkaline conditions to form a hydrolytically stable product, CGA 193469.	1451540

Property	Test substance	Value^2	Transformation products	Comments	Reference
		9 15 0.15 **9 25 0.07** 9 40 0.02			
Phototransformation in soil	CGA 184927	DT_{50} (1 d dry sterile): 13.2 d DT_{50} (10 d wet non-sterile): 0.4 d DT_{50} (3 d wet non-sterile): 0.07 d DT_{50} (1 d wet non-sterile): 0.03 d DT_{50} (1 d dark control): 0.02 d Phototransformation was similar in the dark control and irradiated samples. Dissipation in dry, microbially-inactive soil (t½ =317 h; 13.2 d) indicates that the main route of disappearance of clodinafop-propargyl was microbially mediated.	Major, Irradiated: CGA 193469: 81.41% AR NER: 38.85% AR CO_2 36.36% AR Major, Dark: CGA 193469	Not expected to be an important route of dissipation of CGA 184927. According to EFSA Report, may contribute to dissipation of CGA 193469.	1128909
Biotransformation					
Biotransformation in aerobic soil	[^{14}C-Phenyl] CGA 184927 and CGA 193469	15°C Sandy loam: DT_{50}: **13 d**; DT_{90}: 43.3 d	Major: NER: 53.7% AR CO_2: 49.3% AR	CGA 184927 and CGA 193469 are non-persistent.	1128918
	[^{14}C-Phenyl] and [^{14}C-Pyridinyl] CGA 184927 and CGA	25°C Sandy loam: DT_{50}: **5.58 d**; DT_{90}: 18.6 d (SFO – combined phenyl and pyridine labels)	Major: Phenyl label NER: 60.8%AR CO_2: 59.0% AR		1128919 and 1128924

Property	Test substance	Value[1]	Transformation products	Comments	Reference
	193469		Major: Pyridine label NER: 57.3% AR CO_2: 60.8% AR		
	[^{14}C-Phenyl] CGA 184927 and CGA 193469	25°C Sandy loam: sterile DT_{50}: 4366 d; DT_{90}: 14503 d (SFO)	Minor: NER: 3.5%AR CO_2: < 0.1% AR	CGA 184927 and CGA 193469 are persistent under sterile condition. Biotransformation is microbially-mediated.	1128919
		25°C Sandy loam: Aerobic/anaerobic DT_{50} and DT_{90} could not be calculated.		CGA 184927 and CGA 1934693 were depleted to 1.5% and 2.5% AR, respectively, at initiation of anaerobic condition.	
Biotransformation in aerobic soil	[^{14}C-Pyridinyl] CGA 184927 and CGA 193469	20°C Sandy loam: Standard German soil 2.2 Neuhofen; 55.9% sand; 38.4% silt; 5.7% clay; 2.7% OC; CEC 10 mmol/z/100 g soil, pH 6.0; microbial biomass = 76, 26 and 25 mg microbial C/100 g dry soil at days 0, 84 and 182, respectively. DT_{50}: 14.3 d; DT_{90}: 62 d ($t_{R\ IORE}$ – **18.6**)	Major: NER: 50.1% AR CO_2: 40.9% AR Unknown Uc: 14.1% AR (56 d); 1.9% AR (end)	CGA 184927 and CGA 193469 are non-persistent to slightly persistent.	1128935

Property	**Test substance**	**Value**[1]	**Transformation products**	**Comments**	**Reference**
		20°C Sandy loam, Mosimannacker; 59.1% sand; 34.7% silt; 6.2% clay; 2.3% OC; CEC 6.3 mmol/z/100g soil; pH 6.9; microbial biomass = 49, 43 and 47 mg microbial C/100 g dry soil at days 0, 84 and 182, respectively. DT_{50}: **10 d**; DT_{90}: 33.3 d (SFO)	Major: NER: 58.2% AR CO_2: 37.5% AR Minor: Unknown Uc: 8.8% AR		
		20°C Silty loam, Strassenacker; 35.5% sand; 56.6% silt; 7.9% clay; 1.4% OC; CEC 8.1 mmol/z/100 g soil; pH 7.4; microbial biomass = 58, 27 and 33 mg microbial C/100 g dry soil at days 0, 84 and 182, respectively. DT_{50}: **12 d**; DT_{90}: 39.8 d (SFO)	Major: NER: 58.0% AR CO_2: 34.3% AR Unknown Uc: 10.4% AR		1128935
Biotransformation in aerobic soil	[^{14}C-Phenyl] and [^{14}C-Pyridinyl] CGA 184927 and CGA 193469	25°C Loamy sand soil from Plaza, North Dakota, USA (77% sand, 16% silt, 7% clay, 1.5% organic carbon (OC), pH 7.5, CEC 16.8 meq/100 g, bulk density 1.24 g/cc, and % moisture at 1/3 bar = 14.5)	Major: (pyridine) NER: 31.7% AR CO_2: 64.8% AR CGA302371: 22.5% AR Minor: (pyridine) CGA193468: 5.1% AR	CGA 184927 and CGA 193469 are slightly persistent. Biotransformation in aerobic soil is a	1451544 and 1451545

Property	Test substance	Value[1]	Transformation products	Comments	Reference
		Pyridine Label: DT_{50}: 1.34 d; DT_{90}: 88.3 d (DFOP – representative slow half-life: **43 d)** **Phenyl Label:** DT_{50}: 1.01 d; DT_{90}: 48 d (DFOP – representative slow half-life: **20.9** d) **Combined label:** DT_{50}: 1.13 d; DT_{90}: 56.9 d (DFOP – representative slow half-life: 25.4 d)	CGA 215010: 1.3% AR CGA 239356: 1.1% AR Major: (phenyl) NER: 43.1% AR CO_2: 65.7% AR CGA193468:10.7 % AR Minor: (phenyl) CGA 215010: 0.9% AR CGA 214111: 0.8% AR	route of dissipation for clodinafop-propargyl.	
Biotransformation in aerobic soil	^{14}C-Pyridinyl-CGA 302371	20°C Loam: Gartnacker, (%sand/silt/clay) 37/53/10; pH 7.30; %OC 1.81 DT_{50}: 8.8 d; DT_{90}: 29 d	Major: NER: 32.8%AR CO_2: 61.8% AR	CGA 302371 is non-persistent	2793579
		20°C Sandy loam: Weide, (% sand/silt/clay) 61/31/7; pH 7.49; % OC 1 DT_{50}: 9.4 d; DT_{90}: 31 d	Major: NER: 36.7%AR CO_2: 53.8% AR		
		20°C loamy sand: Pappelacker, % sand/silt/clay) 71/23/6; pH 7.47; % OC 1.56	Major: NER: 35.2%AR CO_2: 61.4% AR		

Property	Test substance	Value[1]	Transformation products	Comments	Reference
		DT_{50}: 12 d; DT_{90}: 41 d			
Biotransformation in anaerobic soil	^{14}C-Pyridinyl-CGA 184927	20°C Silt loam soil: Gartnacker, (% sand/silt/clay) 42/48/10; pH 7.28; % OC 1.86; CEC 12.67 DT_{50}: 2824 d; DT_{90}: 9381d	Major: NER: 3.9%AR CO_2: 0.18% AR	CGA 184927 and CGA 193469 are persistent in anaerobic soil	2793579
Mobility					
Adsorption/desorption in soil	CGA 184927 and major soil transformation products	CGA 184927 Eleven soils: K_d: 0.17–352 mL/g; K_{oc}: 34.7–2737 mL/g	CGA 193469 Thirteen soils: K_d: 0.18–1.58 mL/g; K_{oc}: 21.6–63.14 mL/g CGA 193468 Nine soils: K_F: 3.95–5.44 $\mu g^{1-1/n} mL^{1/n} g^{-1}$; K_{FOC}: 238–365 $\mu g^{1-1/n} mL^{1/n} g^{-1}$; 1/n: 0.73–0.815; K_d: 1.02–8.713 mL/g; K_{oc}: 231–510.8 mL/g CGA 302371	CGA 184927 is classified as having very high to slight potential for mobility in soil. CGA 193469 and CGA 302371 are classified as having very high to high potential for mobility in soil. CGA 193468 is classified as having moderate to low potential for mobility in soil.	1128913 1451551 1451552 1451553 1451554 1451555 1451556

Property	Test substance	Value[1]	Transformation products	Comments	Reference
			Nine soils: K_d: 0.26–1.68 mL/g; K_{oc}: 22.64–84.36 mL/g		
Soil Leaching	[^{14}C-Phenyl] and [^{14}C-Pyridinyl] CGA 184927	28-day aged residue, leached for 16 days with 200 mm water. Leachate: Phenyl: 0.06–0.46% AR Pyridine: 0.16–0.88% AR Eluted soil column: CGA 184927 and CGA 193469 = not detectable in 0–4 cm	Major, both labels NER: 51.62–63.2% AR CO_2:25.1–-38.2% AR Unknown: 6.48–10.6% AR (pyridine) Unknown: 4.52–5.33% AR (phenyl)	Low potential for leaching.	1128915 1128916
		28-day aged residue, leached for 45 days with 508 mm water. Leachate: Phenyl: 1.70–2.13%AR Pyridine: 2.01–4.36%AR Eluted soil column: CGA 184927 and CGA 193469 not detectable in 0–4 cm			1128916
Lysimeter/ field leaching	TOPIK 240 EC at 60 g a.i./ha.	Two locations in United Kingdom (62.2% sand, pH 7.0, OC% 2.3) and clay soil (30% sand, pH 7.3, OC% 1.7); treatment of winter wheat at 60 a.i./ha CGA 184927 not detected in groundwater, surface run-off and soil	CGA 193469 detected in surface run-off at 0.08–0.10 µg/L. CGA 193469 detected in groundwater at 25-cm depth in sand soil (at	CGA 193469 more mobile than CGA 184927 especially in sandy soil.	2793579

Property	Test substance	Value[1]	Transformation products	Comments	Reference
		columns (>0–5cm)	1.66µg/L) and in clay soil (range of 0.07 9.37µg/L) CGA 193469 detected in 0–5 cm depth in clay soil; and in 0–10 cm of sand soil cropped with winter wheat EFSA determined DT_{50} = 19 and 33 days in the sand and clay soil, respectively. CGA 302371 detected only on day 90.		
Volatilization	Not required based on the low vapour pressure (3.19×10-6 Pa at 25 °C) and Henry's law constant (2.8×10-4 Pa m³/mol at 20°C).				
Field studies					
Field dissipation in Canada and the United States	CGA 184927 in 100 g a.i./L formulation and 240 g a.i./L formulations, A781 6A formulation and Horizon 240 EC.	Several bare plots at 2 sites in Saskatchewan and Alberta, Canada. CGA 184927 was not detected.	Major: CGA193469 was found (at 14µg/kg) up to 30 cm soil depth.		1136132 1136133
	Discover Herbicide 240 EC	CGA 184927 not detected. CGA 193469 detected down to 15 cm.	Wheat plot: $t_{R\ IORE}$ 1.33 d (CGA184927 and CGA193469) slow t½: 253 d (CGA 185072 and	CGA184 and CGA193469 are non-persistent under the tested terrestrial field conditions.	1451557

Property	Test substance	Value[1]	Transformation products	Comments	Reference
			CGA153433)		
		CGA 184927 not detected. CGA 193469 detected down to 30 cm	Bare plot: $t_{R\ IORE}$ 3.1 d (CGA 184927 +CGA193469) slow t½: 936 d (CGA 185072 + CGA153433)	Evidence of vertical movement of the CGA193469 at low concentrations. No significant carryover of residues into the next growing season.	

[1] Kinetics models: SFO = single first-order; IORE = indeterminate order rate equation; DFOP = double first order in parallel. **Bold** = values used in fate characterization

Table 2a Leachability assessment of clodianfop-propargyl (CGA 184927) based on classification system of Cohen *et al.* (1984)

Property	Criteria of Cohen *et al.* (1984) indicating a potential for leaching	Value	Meets criterion for leaching
Solubility in water	> 30 mg/L	4 mg/L	No
K_d	< 5 and usually < 1 or 2	K_d: 0.168–352 mL/g	No
K_{oc}	< 300	K_{oc}: 34.7–2737 mL/g	No
Henry's law constant	$< 10^{-2}$ atm m³/mol	2.8×10^{-4} Pa m³/mol	Yes
pK_a	Negatively charged (either fully or partially) at ambient pH	None (pH 2–10): No dissociation at environmentally relevant pH	No
Hydrolysis half-life	> 20 weeks (> 140 days)	pH4 t½=17.9 d at 25°C pH 5 t½=26.8 d at 25°C	No

Property	Criteria of Cohen *et al.* (1984) indicating a potential for leaching	Value	Meets criterion for leaching
		pH 7 $t_{1/2}$=4.8 d at 25°C pH 9 $t_{1/2}$=0.07 d at 25°C	
Soil phototransformation half-life	> 1 week (> 7 days)	Stable	Yes
Half-life in soil	> 2 to 3 weeks (> 14 to 21 days)	< 2 days	No

Table 2b Leachability assessment of CGA 193469 based on classification system of Cohen *et al.* (1984)

Property	Criteria of Cohen *et al.* (1984) indicating a potential for leaching	Value	Meets criterion for leaching
Solubility in water	> 30 mg/L	> 560	Yes
K_d	< 5 and usually < 1 or 2	K_d: 0.37–1.58 mL/g	Yes
K_{oc}	< 300	K_{oc}: 21.6–63.14 mL/g	Yes
Henry's law constant	$< 10^{-2}$ atm m^3/mol	2.163×10^{-5}	Yes
pK_a	Negatively charged (either fully or partially) at ambient pH	2.91 (acidic)	No
Hydrolysis half-life	> 20 weeks (> 140 days)	Stable	Yes
Soil phototransformation half-life	> 1 week (> 7 days)	Stable	Yes
Half-life in soil	> 2 to 3 weeks (> 14 to 21 days)	20.9 days (80th percentile of 6 values)	Yes

Table 3 **PMRA Uncertainty Factors and Levels of Concern**

Organism Group	Exposure	Endpoint	Uncertainty Factor when using LD_{50}, LC_{50} or EC_{50}	Level of concern
Earthworm	Acute	LC_{50}	0.5	1
Bees	Acute	LD_{50} or LC_{50}	none	0.4
Beneficial Insects	Acute	LR_{50}	none	2
Birds/Mammals	Acute oral	LD_{50}	0.1	1
	Acute dietary	5-day LD_{50} (LC_{50} converted to dose)	0.1	1
	Chronic	NOEL (NOEC converted to dose)	none	1
Vascular Plants	Acute	EC_{25}	none	1
Aquatic plants/pelagic invertebrates/benthic invertebrates	Acute	EC_{50}	0.5	1
	Chronic	NOEC	none	1
Fish	Acute	LC_{50}	0.1	1
	Chronic	NOEC	none	1
Amphibians	Acute	fish LC_{50}	0.1	1
	Chronic	fish NOEC	none	1

Table 4 Toxicity to Non-Target Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity^{1,2}	PMRA#
Terrestrial Organisms					
Invertebrates					
Earthworm, *Eisenia fetida*	14-d Acute	Clodinafop-propargyl	LC_{50}: 18.53 mg a.i./kg soil	No classification	1136140
		Clodinafop-propargyl 24 EC (analytical purity 22.77%)	LC_{50}: **14.05 mg a.i./kg soil** NOEC: 11.36 mg a.i./kg	No classification	1816160
		Clodinafop-propargyl (purity 93.7%)	14-day LC_{50} = 210 mg a.i./kg NOEC: 62.5 mg a.i./kg	No classification	2793581
		CGA 193469 (purity 95.4%)	14-day LC_{50} > 1000 mg a.i./kg NOEC: 556 mg a i/kg	No classification	2793581
		CGA 193468 (purity 97%)	14-day LC_{50} = 401 mg a.i./kg NOEC= 195.1 mg a.i./kg	No classification	
		CGA 302371 (purity 99%)	14-day LC_{50} = 408 mg a.i./kg NOEC: 171 mg a.i./kg	No classification	
		Topik 100 EC	14-day LC_{50} = 28.3 mg a.i./kg NOEC = 16.6 mg a.i./kg	No classification	
Bees					
Honeybee, *Apis mellifera*	48-h Oral	Clodinafop-propargyl 24 EC (purity = 22.7%)	LD_{50} **11.02 µg a.i./bee**	Relatively non-toxic	1816158

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1,2]	PMRA#
	48-h Contact		LD_{50}: > 22.77 µg a.i./bee	Relatively non-toxic	1816159
	48-h Oral and Contact	Clodinafop-propargyl (purity = 97.9%)	LD_{50}: > 104 µg a.i./bee	Relatively non-toxic	2346280
	48-h Oral	Topik 100 EC (purity = 99.2 g a.i/L)	LD_{50} 17.8 µg a.i./bee	Relatively non-toxic	2793581
	48-h Contact		LD_{50} **40.9 µg a.i./bee**	Relatively non-toxic	
Beneficial Arthropods					
Predatory mite, *Typhlodromus pyri*	14-d Contact, Glass plates (screening level)	Clodinafop-propargyl 240 EC (formulation containing 99.2 g CGA 184927/L and 24.4 g CGA 185072/L)	LR_{50} 30.9 g a.i/ha NOER: 3.75 g a.i/ha	No classification	2346283
Parasitoid wasp, *Aphidius rhopalosiphi*	48h-Contact, Glass plates (screening level)		LR_{50} 6.28 g a.i/ha NOER: 3.75 g a.i/ha	No classification	2346281
Predatory mite, *Typhlodromus pyri*	14-d Contact, Glass plates (screening level)	A 7957 C (formulation containing 99.2 g CGA 184927/L and 24.4 g CGA 185072/L)	LR_{50}: **20 g CGA 184927/ha** NOER = 16 g CGA 184927/ha	No classification	2349859
Parasitoid wasp, *Aphidius rhopalosiphi*	48h-Contact, Glass plates (screening level)		LR_{50}: **3.14g a.i./ha** NOER = 0.5 g a.i./ha	No classification	2349863
Lacewing, *Chrysoperla carnea*	14-d Contact, Glass plates		LR_{50}: > 60 g a.i./ha NOER = 60 g a.i./ha (field rate)	No classification	2349862
Predatory mite, *Typhlodromus pyri*	14-d extended laboratory test (exposure to dry residues in conjunction with surfactant	A 7957 C (formulation containing 99.2 g CGA 184927/L and 24.4 g CGA 185072/L) + 0.5%	LR_{50}: **> 90 g a.i./ha** NOER = 90 g a.i./ha (highest rate tested)	No classification	2349860

Organism	**Exposure**	**Test substance**	**Endpoint value**	**Degree of toxicity**[1,2]	**PMRA#**
	Actipron on treated bean leaves	Actipron			
Parasitoid wasp, *Aphidius rhopalosiphi*	48-h extended laboratory test (exposure to dry residues on treated barley seedlings)	A 7957 C (formulation containing 99.9 g CGA 184927/L and 2584 g CGA 185072/L)	LR$_{50}$: **> 135 g a.i./ha** NOER = 135 g a.i./ha (highest rate tested)	No classification	2349864
Carabid Beetle, *Poecilus cupreus*	14-d Laboratory study	A 7957 C (formulation containing 99.2 g CGA 184927/L and 24.4 g CGA 185072/L)	LR$_{50}$: **> 60 g a.i./ha** NOER = 60 g a.i./ha (field rate)	No classification	2349861
Rove Beetle, *Aleochara bilineata*	28-d extended laboratory study (residual contact exposure to treated soil)	A 7957 C (formulation containing 99.9 g CGA 184927/L and 2584 g CGA 185072/L) + 0.5% Actipron	LR$_{50}$: > 90 g a.i./ha NOER = 60 g a.i./ha	No classification	2349865
	71-d rate-response test under extended laboratory conditions (exposure to dried residue on treated soil)	Clodinafop-propargy 240 EC	LR$_{50}$: > 120 g a.i./ha NOER = 120 g a.i./ha	No classification	2346287
Birds					
Mallard duck, *Anas platyrhynchos*	Acute	Clodinafop-propagyl (93.7% a.i.)	LD$_{50}$: > 1874 mg a.i./kg bw NOEC: 1874 mg a.i./kg bw	Slightly toxic	2793581
	5-d Dietary	Clodinafop-propagyl (94.2% a.i.)	LC$_{50}$: > 1002 mg a.i./kg bw/day NOEC: 170 mg a.i./kg bw/d	Slightly toxic	
	24-w Reproduction	Clodinafop-propagyl (94.2%	NOEC: 471 mg a.i./kg diet (highest	No classification	1149094

Organism	**Exposure**	**Test substance**	**Endpoint value**	**Degree of toxicity[1,2]**	**PMRA#**
		a.i.)	concentration tested) (NOEL: 82 mg a.i./kg bw/d)		
Northern bobwhite quail, *Colinus virginianus*	Acute	Clodinafop-propagyl (93.7% a.i.)	LD_{50} 1363 mg a.i./kg bw NOEC: 683 mg a.i./kg bw	Slightly toxic	2793581
	5-d Dietary	Clodinafop-propagyl (94.2% a.i.)	LC_{50}: **> 980 mg a.i./kg bw/day** NOEC: 236 mg a.i./kg bw/d	Slightly toxic	
	24-w Reproduction	Clodinafop-propagyl (94.2% a.i.)	NOEC: 471 mg a.i./kg diet (highest concentration tested) (NOEL: **43** **mg a.i./kg bw/d)**	No classification	1149095
Japanese quail, *Coturnix japonica*	Acute	Clodinafop-propargyl 24 EC (22.77% a.i.)	LD_{50}: **> 455 mg a.i./kg bw** (the highest concentration tested) NOEC: 455 mg a.i./kg bw	Moderately toxic	1816162
Mammals					
Rat	Acute	CGA 184927	LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic	1128883
			LD_{50} > 1829 mg/kg bw	practically non-toxic	1169346
	2-generation Reproduction	CGA 184927 Purity = 93.7%	Parental Toxicity NOAEL = **3.21 mg/kg bw/day** (♂) NOAEL = 3.77 mg/kg bw/day (♀)	No classification	1239131 1128906

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity^{1,2}	PMRA#
			Reproductive toxicity NOAEL = 31.7/37.5 mg/kg bw/day (♂/♀)		
	Prenatal Developmental (Gavage)	CGA 184927 Purity = 93.7% 6♀/group 0, 5, 40, 80, 160 mg/kg bw/day from GD 6 to 15		No classification	1158416
		Purity = 93.7% 25♀/group 0, 5, 40, 160 mg/kg bw/day from GD 6 to 15 (Necropsy on GD 20)	Maternal Toxicity NOAEL = 40 mg/kg bw/day Developmental Toxicity NOAEL = ND LOAEL = 5 mg/kg bw/day		1158475 1239120 1128906
Vascular plants					
Monocot and dicot crop species (onion, ryegrass, oat, lettuce, cucumber, carrot, radish, soybean, tomato, corn)	21-d Seedling emergence	clodinafop-propargyl 24EC (purity 22.3%/5.79% active ingredients of CGA 184927 and CGA 185072)	Most sensitive of 10 species: ER_{25}: **35 g a.i./ha** NOEC:25 g a.i./ha (dried shoot weight in ryegrass, *Lolium perenne*)	No classification	1451569
Two monocot (onion, *Allium cepa*; and oat, *Avena sativa*) and four dicot (oilseed rape, *Brassica napus*; carrot,		Topik 100 EC (99.9 g/L clodinafop-propargyl, 25.8 g/L CGA 185072)	Most sensitive of 6 species: ER_{50}: > 60 g CGA 184927/ha NOER: 15 g GF-	No classification	2793581

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1,2]	PMRA#
Daucus carota; lettuce, *Lactuca sativa*, pea, *Pisum sativum*)			2687/ha (shoot dry weight in lettuce, *Lactuca sativa*)		
Four monocot species (onion, *Allium cepa*, oat, *Avena sativa*, ryegrass, *Lolium perenne*, and corn, *Zea* mays) and six dicot species (cucumber, *Cucumis sativus*, carrot, *Daucus carota*, soybean, *Glycine max*, lettuce, *Lactuca sativa*, tomato, *Lycopersicon esculentum*, and radish, *Raphanus sativus)*		CGA-193469 (purity 94.1%)	Most sensitive of 11 species: ER_{25}: **17.2 g a.i./ha** NOER: 17.7 g a.i./ha (biomass in ryegrass, *Lolium perenne*)	No classification	1451571
Monocot and dicot crop species (onion, ryegrass, oat, lettuce, cucumber, carrot, radish, soybean, tomato, corn)	21-d Vegetative vigor	clodinafop-propargyl 24EC (purity 22.3%/5.79% active ingredients of CGA 184927 and CGA 185072)	Most sensitive of 10 species: ER_{25}: **5.41 g a.i./ha** NOEC:3.13 g a.i./ha (vigor phytotoxic effects in corn, *Zea mays*)	No classification	1451569
Two monocot (onion, *Allium cepa*; and oat, *Avena sativa*) and four dicot (oilseed rape, *Brassica napus*; carrot, *Daucus carota*; lettuce, *Lactuca sativa*, pea, *Pisum sativum*)		Topik 100 EC (99.9 g/L clodinafop-propargyl, 25.8 g/L CGA 185072)	Most senstive of 6 species: ER_{50}: 15 g CGA 184927/ha NOER: 3.7 g CGA 184927/ha (shoot dry weight in oat, *Avena sativa*)	No classification	2793581
Four monocot species (onion, *Allium cepa*, oat, *Avena sativa*,		CGA-193469 (purity 94.1%)	Most sensitive of 11 species:	No classification	1451570

Organism	**Exposure**	**Test substance**	**Endpoint value**	**Degree of toxicity**^{1,2}	**PMRA#**
ryegrass, *Lolium perenne*, and corn, *Zea mays*) and six dicot species (cucumber, *Cucumis sativus*, carrot, *Daucus carota*, soybean, *Glycine max*, lettuce, *Lactuca sativa*, tomato, *Lycopersicon esculentum*, and radish, *Raphanus sativus*)			ER_{25}: **35.1 g a.i./ha** NOER: 17.7 g/ha (biomass in corn, *Zea mays*)		
Aquatic Organisms					
Freshwater Invertebrates					
Daphnia magna	48-h Acute	CGA 184927 94.7% a.i.	EC_{50}: > 2.00 mg a.i./L (Mean measured concentration)	Could not be classified because of non-definitive endpoint	1451560
	48-h Acute (static)	CGA 184927 (purity 93.7%) in DMF	LC_{50}: > 4 mg/L (based on limit solubility)	Could not be classified because of non-definitive endpoint	1924514 2793581
	48-h Acute Semi-static, limit test	CGA 193469 (purity 86.4%)	EC_{50}: **> 9.2 mg/L** (Mean measured concentration)	Could not be classified because of non-definitive endpoint	1149096
	48-h Acute	CGA 302371 (purity 99%)	EC_{50}: **> 96.32 mg/L** NOEC: 54.0 mg/L (Measured end concentration	Could not be classified because of non-definitive endpoint	1169633
	48-h Acute Static	CGA 193468 (purity 98%)	EC_{50}: **12 mg a.i./L** (nominal concentration)	Slightly toxic	2793581
	48-h Acute	Topik 240 EC (21.8% CGA	EC_{50}: 5.2 mg a.i./L NOEC: 2.8 mg a.i./L	Moderately toxic	1136141

Organism	**Exposure**	**Test substance**	**Endpoint value**	**Degree of toxicity^{1,2}**	**PMRA#**
		184927, 5.6% CGA 185072 and 1% additive Assist A-8386A)	(Initial measured concentration)		
	48-h Acute	Clodinafop-propargyl 24 EC (containing 22.67% CGA 184927	EC_{50}: **0.05 mg** a.i./L NOEC: 0.01 mg a.i./L (nominal concentrations)	Very highly toxic	1816161
	48-h Acute (Static)	Topik 100 EC formulation (99.2 g CGA 184927 /L, 24.4 g CGA 185072/L	EC_{50}: 0.37 mg a.i./L NOEC: 0.19 mg a.i./L (nominal concentrations)	Highly toxic	2793581
	21-d Chronic	CGA 184927 (purity 94.2%)	NOEC: **0.23 mg a.i./L** (End point adult survival) (mean measured concentration)	No classification	1451562
	21-d Chronic	CGA 184927(purity 93.7%) in DMF	NOEC:< 0.039 mg a.i/L (nominal concentration)	No classification	1924514 2793581
	22-d Chronic	CGA 193469 (purity 99.3%)	NOEC: **0.16** mg/L (Based on effects on reproduction) (mean measured concentration)	No classification	1451563
Sediment dwelling invertebrate, *Chironomus riparius*	28-d Chronic, spiked water	CGA 184927 (purity 93.6%)	NOEC: **0.78 mg/L** in overlying water (death of larvae in the highest initial measured test concentration)	No classification	2349866
Fish					
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute	CGA 184927 (purity 94.7%)	LC_{50}: **0.31 mg a.i./L** (mean measured concentration)	Highly toxic	1451564
		CGA 302371 (purity 99%)	LC_{50}: > **100 mg/L** (nominal concentration)	Could not be classified because of non-definitive	1166259

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1,2]	PMRA#
				endpoint	
	96-h Acute	Topik 240 EC (containing 21.8% CGA 184927 +5.6% CGA 185072+1.0% Additive Assist A-8386 A)	LC_{50}: 4.9 mg a.i./L (based on nominal concentration) NOEC: 3.2 mg/L	Moderately toxic	1136137
	96-h Acute (static)	Topik 100 EC formulation (99.2 g CGA 184927/L, 24.4 g CGA 185072/L)	LC_{50}: 1.0 mg a.i./L (95% CI 0.83–1.3) NOEC: 0.35 mg/L (nominal concentrations)	Highly toxic	2793581
	96-h Acute (flow-through)	CGA 184927 (purity 93.7%) in DMF	LC_{50}: 0.39 mg a.i/L (95%CL: 0.32-0.48) (mean measured concentration)	Highly toxic	1924514 2793581
	96-h Acute (static)	CGA 193469 (purity 90.4%) ARKOPAL (alkylphenol-polyglycol-ether)	LC_{50}: > 90.4 mg/L (mean measured concentration)	Could not be classified because of non-definitive endpoint	
	96-h Acute Static	CGA 193468 (purity 98%)	LC_{50}: **5.7 mg a.i./L** (nominal concentration)	Moderately toxic	
	21-d Short-term reproduction	CGA 184927 (purity 94.2%)	NOEC: **0.10** mg a.i./L (survival and symptoms)	No classification	
Common carp, *Cyprinus carpio*	96-h Acute	CGA 184927 (purity 93.7%)	LC_{50}: 0.43 mg/L (mean measured concetration)	Highly toxic	
	96-h Acute	Topik 240 EC (containing 21.8% CGA 184927 +5.6% CGA 185072 + 1.0% Additive Assist A-8386 A)	LC_{50}: 6.3 mg a.i./L NOEC: 1.8 mg/L (nominal concentrations)	Moderately toxic	1136138
	96-h Acute	Clodinafop-propargyl 24 EC	LC_{50}: 0.62 mg a.i./L	Highly toxic	1816163

Organism	**Exposure**	**Test substance**	**Endpoint value**	**Degree of toxicity**[1,2]	**PMRA#**
		(containing 22.7% CGA 184927	NOEC: 0.23 mga.i./L (nominal concentration)		
	96-h Acute (Static)	CGA 193469 (purity 90.4%) ARKOPAL (alkylphenol-polyglycol-ether)	LC_{50}: **>76 mg/L** (mean measured concentration)	Could not be classified because of non-definitive endpoint	1924514 2793581
Bluegill sunfish, *Lepomis macrochirus*.	96-h Acute	CGA 184927 (purity 93.7%)	LC_{50}: **0.21 mg a.i./L** (mean measured concentration)	Highly toxic	1128925
	96-h Acute (Static)	CGA 193469 (purity 90.4%) ARKOPAL (alkylphenol-polyglycol-ether)	LC_{50}: > 76 mg/L (mean measured concentration)	Could not be classified because of non-definitive endpoint	1924514 2793581
Catfish, *Ictalurus punctatus*	96-h Acute	CGA 184927 (purity 93.7%)	LC_{50}: 0.46 mg/L (95%CL: 0.35–0.62)	Highly toxic	
	96-h Acute (Static)	CGA 193469 (purity 90.4%) ARKOPAL (alkylphenol-polyglycol-ether)	LC_{50}: > 76 mg/L (mean measured concentration)	Could not be classified because of non-definitive endpoint	
Fathead minnow *Pimephales promelas*	Chronic (early life stage)	CGA 184927 (purity 99.0%)	NOEC: **0.014** mg a.i./L based on effects to body weight at 0.024 mg a.i./L. Other effects observed in the study were reductions in hatching success, survival, and body length	No classification	2630391
Algae					
Green algae, *Pseudokirchneriella subcapitata*	96-h Acute (Static)	CGA 184927 (purity 94.7%)	E_bC_{50}: > 3.9 mg a.i./L (based on initial measured concentration)	Could not be classified because of non-definitive	1451568

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1,2]	PMRA#
				endpoint	
	72-h Acute	clodinafop-propargyl 24 EC (22.77% CGA 184927	E_bC_{50}: 0.43 mg a.i./L 1.89 mg clodinafop-propargyl 24EC/L Most sensitive endpoint = growth inhibition (nominal concentration)	No classification	1816157
	72-h Acute static	CGA 302371 (purity 99%)	Most sensitive endpoint: area under the growth curve E_bC_{50}: **30 mg/L** (mean measured concentration)	No classification	1166269
	72-h Acute (static)	Topik 100 EC formulation (99.2 g CGA 184927 /L, 24.4 g CGA 185072/L)	E_bC_{50}: 0.45 mg a.i./L E_rC_{50}: > 0.85 mg a.i./L NOEC: 0.17 mg a.i./L (nominal concentrations)	No classification	2793581
Green algae, *Scenedesmus subspicatus*	96-h Acute	CGA 184927 (purity 94.2%) in ARKOPAL	Most sensitive endpoint: areas under the curve EC_{50}: 1.4 mg a.i./L (highest measured test concentration without precipitate)	No classification	1128927
	72-h Acute (static)	CGA 184927 (purity 94.2%) in cremophor	Most sensitive endpoint: area under the curve E_bC_{50}: 1.7 mg/L (biomass) based on mean measured concentration	No classification	1451566
	72-h Acute (static)	CGA 184927 (purity 93.7%) In DMF	E_bC_{50}: > 4 mg/L Set by EFSA based on solubility of test substance	No classification	2793581

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1,2]	PMRA#
	96-h Acute (static)	CGA 193469 (purity 86.4%)	Most sensitive endpoint: area under the growth curve EC_{50}: 65 mg/L (nominal concentration)	No classification	1128930
	72-h Acute (static)	CGA 193468 (purity 98%)	E_rC_{50}: **2.4 mg/L** (nominal concentration)	No classification	2793581
	96-h Acute	Topik 240 EC (containing 21.8% CGA 184927 + 5.6% CGA 185072 + 1.0% Additive Assist A-8386 A)	Most sensitive endpoint: area under the growth curve LC_{50}: 5.3 mg a.i./L NOEC: 1.8 mg/L (nominal concentration)	No classification	1136144
Blue-green algae, *Microcystis aeruginosa*	120-h Acute (static)	CGA 184927 (purity 94.2%) In ARKOPAL	EC_{50}: 3.1 mg a.i./L (highest measured concentration without precipitation)	No classification	1128929
	120-h Acute	CGA 193469 (purity 86.4%)	Most sensitive endpoint: area under the growth curve EC_{50}: **49 mg/L** (nominal concentration)	No classification	1128932
	96-h Acute (static)	Topik 240 EC (containing 21.8% CGA 184927 + 5.6% CGA 185072 + 1.0% Additive Assist A-8386 A)	Most sensitive endpoint: area under the growth curve LC_{50}: **0.1** mg a.i. a.i./L(highest measured concentration without precipitation) NOEC: 0.1 mg a.i./L	No classification	1136145

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity^{1,2}	PMRA#
Blue-green alga, *Anabaena flos-aquae*	120-h Acute	CGA 184927 (purity 94.7%)	Most sensitive endpoint: growth rate EC_{50}: > 3.6 mg a.i./L (initial measured concentrations)	No classification	1451567
Diatom, *Navicula pelliculosa*	96-h Acute (static)	CGA 184927 (purity 94.2%)	Most sensitive endpoint: area under the curve EC_{50}: **0.04 mg a.i./L** (highest measured concentration without precipitation)	No classification	1128928
	96-h Acute (static)	CGA 193469 (purity 86.4%)	Most sensitive endpoint: area under the growth curve E_bC_{50}: 76 mg/L (nominal concentrations)	No classification	1128931
	96-h Acute	Topik 240 EC (containing 21.8% CGA 184927 +5.6% CGA 185072+1.0% Additive Assist A-8386 A)	Most sensitive endpoint: area under the growth curve LC_{50}: **0.5 mg a.i./L** (highest measured concentration without precipitation) NOEC: < 4.8 mg a.i./L	No classification	1136146
Aquatic plants					
Monocot vascular plant, duckweed, *Lemna gibba*	14-d Dissolved	CGA 184927 (purity 94.2%)	Most sensitive endpoint: frond density and biomass EC_{50}: > 2.4 mg a.i./L (initial measured concentration)	No classification	1451572
	14-d semi-static (static)	CGA 193469 (purity 86.4%)	EC_{50}: **> 4.5 mg/L** (mean measured concentrations)	No classification	2793581

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1,2]	PMRA#
	7-d Dissolved	Topik 240 EC (containing 21.8% CGA 184927 +5.6% CGA 185072+1.0% Additive Assist A-8386 A)	EC_{50}: > 45 mg a.i./L NOEC: 45 mg a.i./L (based on nominal concentration)	No classification	1136150
Great manna grass, *Glyceria maxima*	14-d Static and 14 days recovery	Topik 240 EC	Most sensitive endpoint: growth rate EC_{50}: 0.15 mg a.i./L NOEC: 0.012 mg a.i./L (based on initial measured concentration) No recovery 14 days after withdrawal of test substance.	No classification	2793581
	56-d microcosm study	CGA 184927	Most sensitive endpoint: shoot length EC_{50}: 0.048 mg a.i./L (nominal concentration)	No classification	2846896
Marine/estuarine species					
Crustacean, mysid shrimp, *Americamysis bahia*	96-h Acute (flow-through)	CGA 184927 (purity 94.7%) in DMF	LC_{50}: 0.82 mg a.i./L (0.68-0.96) (mean measured concentration)	Highly toxic	2793581
Mollusk, Eastern oyster, *Crassostrea virginica*	96-h Acute (flow-through)	CGA 184927 (purity 94.7%) in DMF	Shell deposition: LC_{50}: 0.77 mg a.i./L (0.57–1.00) (mean measured concentration)	Highly toxic	2793581
[1] Atkins *et al.* (1981) for bees and US EPA classification for others, where applicable					
[2] US EPA classification, where applicable. **Bold** = values used in risk assessment.					

Table 5 Screening Level Risk Assessment on Non-Target Species

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern
Terrestrial Organisms					
CGA 184927					
Invertebrates					
Earthworm	Acute	$LC_{50}/2$ 14.05 mg a.i./kg soil	0.0312 mg a.i./kg soil	0.004	Not exceeded
Bee	Contact	LD_{50}: 40.9 µg a.i./bee	0.0702 kg a.i./ha × 2.4 µg a.i./bee per kg/ha = 0.16848 µg a.i./bee	0.004	Not exceeded
	Oral	LD_{50}: 11.02 µg a.i./bee	0.0702 kg a.i./ha × 29 µg a.i./bee per kg/ha = 2.036 µg a.i./bee	0.185	Not exceeded
	Brood/hive	Risk is not expected from exposure to clodinafop-propargyl based on the mode of action and lack of effects observed for adult bees.			
Predatory arthropod, *Typhlodromus pyri*	Contact, glass plate	LR_{50}: 20 g a.i./ha	In-field: 70.2 g a.i./ha	In-field: **3.51**	**Exceeded**
			Off-field (aerial appl., 17% drift): 11.93 g a.i./ha	Off-field (aerial): 0.6	Not exceeded
			Off-field (ground appl., 6% drift): 4.2 g a.i./ha	Off-field (ground): 0.2	Not exceeded
	14-d extended laboratory test (exposure to dry	LR_{50}: > 90 g a.i./ha (highest rate tested)	In-field: 70.2 g a.i./ha	In-field: < 0.78	Not exceeded

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern
	residues in conjunction with surfactant Actipron on treated bean leaves)				
Parasitoid arthropod, *Aphidius rhopalosiphi*	Contact, glass plate	$LR_{50:}$ 3.14 g a.i./ha	In-field: 70.2 g a.i./ha	In-field: **22.36**	**Exceeded**
			Off-field (aerial appl., 17% drift): 11.93 g a.i./ha	Off-field (aerial): **3.8**	**Exceeded**
			Off-field (ground appl., 6% drift): 4.2 g a.i./ha	Off-field (ground): 1.34	Not exceeded
	48-h extended laboratory test (exposure to dry residues on treated barley seedlings)	$LR_{50:}$ >315 g a.i./ha (highest rate tested)	In-field: 70.2 g a.i./ha	In-field: < 0.52	Not exceeded
Terrestrial invertebrate, *Aleochara bilineata*	Dried residue on treated soil	71-d LR_{50}> 120 mg a.i./kg soil	0.0312 mg a.i./kg soil	< 0.0002	Not exceeded
Vascular plants					
Vascular plant	Seedling emergence	ER_{25} = 35 g a.i./ha	In-field: 70.2 g a.i./ha	In-field: **2.0**	**Exceeded**
			Off-field (aerial appl., 17% drift): 11.93 g a.i./ha	Off-field (aerial): 0.34	Not exceeded

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern
			Off-field (ground appl., 6% drift): 4.2 g a.i./ha	Off-field (ground): 0.12	Not exceeded
	Vegetative vigour	ER_{25} = 5.41 g a.i./ha	In-field: 70.2 g a.i./ha	In-field: **12.98**	**Exceeded**
			Off-field (aerial appl., 17% drift): 11.93 g a.i./ha	Off-field (aerial): **2.21**	**Exceeded**
			Off-field (ground appl., 6% drift): 4.2 g a.i./ha	Off-field (ground): 0.77	Not exceeded
CGA 193469					
Earthworms	Acute	$LC_{50}/2$ >1000 mg/kg soil	0.0312 mg/kg soil	<0.0001	Not exceeded
Vascular plants	Seedling emergence	$ER_{50}/2$ = 17.2 g/ha	In-field: 70.2 g/ha	In-field: **4.08**	**Exceeded**
			Off-field (aerial appl., 17% drift): 11.93 g/ha	Off-field (aerial): 0.69	Not exceeded
			Off-field (ground appl., 6% drift): 4.21 g/ha	Off-field (ground): 0.24	Not exceeded
Vascular plants	Vegetative vigour	$ER_{50}/2$ = 35.1 g/ha	In-field: 70.2 g/ha	In-field: **2.0**	**Exceeded**
			Off-field (aerial appl., 17% drift): 11.93 g/ha	Off-field (aerial): 0.34	Not exceeded

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern
			Off-field (ground appl., 6% drift): 4.21 g/ha	Off-field (ground): 0.12	Not exceeded
CGA 302371					
Earthworms	Acute	LC_{50}/2: 408 mg/kg soil	0.0312 mg/kg soil	0.0001	Not exceeded
CGA 193468					
Earthworms	Acute	LC_{50}/2: 401 mg/kg soil	0.0312 mg/kg soil	0.002	Not exceeded
Aquatic Organisms					
Invertebrates (*Daphnia magna*)	Acute	EC_{50}/2 = 0.025	0.0087	0.35	Not exceeded
	Chronic	NOEC = 0.23	0.0087	0.039	Not exceeded
Fish	Acute	LC_{50}/10 = 0.021	0.0087	0.414	Not exceeded
	Early-life stage	NOEC = 0.014	0.0087	0.62	Not exceeded
	Short-term reproduction	NOEC = 0.1	0.0087	0.087	Not exceeded
Amphibians (fish end-points)	Acute	LC_{50}/10 = 0.021	0.046	**2.19**	**Exceeded**
	chronic	NOEC = 0.014	0.046	**3.29**	**Exceeded**
Algae	Acute	EC_{50}/2 = 0.02	0.0087	0.44	Not exceeded
Vascular plants (monocot, *Glyceria maxima*)	Dissolved	EC_{50}/2 = 0.024	0.0087	0.36	Not exceeded

Organism	**Exposure**	**Endpoint Value**	**EEC**	**RQ**	**Level of Concern**
Marine species					
Crustacean	Acute	$LC_{50}/2 = 0.41$	0.0087	0.02	Not exceeded
Mollusk	Acute	$EC_{50}/2 = 0.385$	0.0087	0.02	Not exceeded
CGA 193469					
Invertebrates (*Daphnia magna*)	Acute	$EC_{50}/2 > 4.6$	0.0087	< 0.002	Not exceeded
	Chronic	NOEC = 0.16	0.0087	0.054	Not exceeded
Fish	Acute	$LC_{50}/10 > 7.6$	0.0087	< 0.001	Not exceeded
Algae	Acute	$EC_{50}/2 = 24.5$	0.0087	0.0003	Not exceeded
Vascular plants (monocot, *Lemna gibba*)	Dissolved	$EC_{50}/2 => 4.5$	0.0087	< 0.004	Not exceeded
CGA 302371					
Invertebrates (*Daphnia magna*)	Acute	$EC_{50}/2 >48.16$	0.0087	< 0.0001	Not exceeded
Fish	Acute	$LC_{50}/10 > 10$	0.0087	< 0.0001	Not exceeded
Algae	Acute	$EC_{50}/2 = 15$	0.0087	0.0006	Not exceeded
CGA 193468					
Invertebrates (*Daphnia magna*)	Acute	$EC_{50}/2 = 6$	0.0087	0.001	Not exceeded

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern
Fish	Acute	LC_{50}/10 = 0.57	0.0087	< 0.02	Not exceeded
Algae	Acute	EC_{50}/2 = 1.2	0.0087	0.007	Not exceeded

Table 6 **Refined Assessment of potential risk from drift of clodinafop-propargyl to aquatic organisms**

Organism	Exposure	Endpoint value	Refined EEC	RQ	Level of Concern
Amphibians (fish end-points)	Acute	EC_{50}/10 = 0.021 mg a.i./L	Aerial appl. (17% drift): 0.0078 mg a.i./L	0.37	Not Exceeded
			Ground appl. (6% drift): 0.0028 mg a.i./L	0.13	Not exceeded
	Chronic	NOEC = 0.014 mg/L	Aerial appl. (17% drift): 0.0078 mg a.i./L	0.56	Not Exceeded
			Ground appl. (6% drift): 0.0028 mg a.i./L	0.20	Not exceeded

Table 7a **Screening level risk assessment of clodinafop-propargyl for birds and mammals: Single foliar application at 70.2 g a.i./ha to Wheat (spring and durum)**

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw) [1]	RQ	Level of Concern
Small Bird (0.02 kg)					
Acute	> 455	Insectivore (small insects)	5.71	< 0.13	Not exceeded
Reproduction	43	Insectivore (small insects)	5.71	0.13	Not exceeded
Medium Sized Bird (0.1 kg)					
Acute	> 455	Insectivore (small insects)	4.46	0.10	Not exceeded

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw) [1]	RQ	Level of Concern
Reproduction	43	Insectivore (small insects)	4.46	0.10	Not exceeded
Large Sized Bird (1 kg)					
Acute	> 455	Herbivore (short grass)	2.88	0.06	Not exceeded
Reproduction	43	Herbivore (short grass)	2.88	0.07	Not exceeded
Small Mammal (0.015 kg)					
Acute	182.90	Insectivore (small insects)	3.29	0.02	Not exceeded
Reproduction	3.21	Insectivore (small insects)	3.29	**1.02**	**Exceeded**
Medium Sized Mammal (0.035 kg)					
Acute	182.90	Herbivore (short grass)	6.37	0.03	Not exceeded
Reproduction	3.21	Herbivore (short grass)	6.37	**1.99**	**Exceeded**
	3.21	Herbivore (long grass)	3.89	**1.21**	**Exceeded**
	3.21	Herbivore (broadleaf plants)	5.90	**1.84**	**Exceeded**
Large Sized Mammal (1 kg)					
Acute	182.90	Herbivore (short grass)	3.41	0.02	Not exceeded
Reproduction	3.21	Herbivore (short grass)	3.41	**1.06**	**Exceeded**

1 EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:

FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:

Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = 0.398 (BW in g) 0.850

All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648 (BW in g) 0.651.

For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235 (BW in g) 0.822

BW: Generic Body Weight

EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

Table 7b Refined risk assessment of clodinafop-propargyl for mammals off-field of application site: Applying 6% spray drift for medium spray ground boom and 17% spray drift for coarse spray aerial application to Wheat (spring and durum)

Toxicity (mg a.i./kg bw/d)		Feeding Guild (food item)	Off-field from ground boom application using medium spray			Off-field from aerial application using coarse spray		
			EDE (mg a.i./kg bw)	RQ	Level of Concern	EDE (mg a.i./kg bw)	RQ	Level of Concern
Small Mammal (0.015 kg)								
Reproduction	3.21	Insectivore (small insects)	0.20	0.06	Not Exceeded	0.56	0.17	Not Exceeded
Medium Sized Mammal (0.035 kg)								
Reproduction	3.21	Herbivore (short grass)	0.38	0.12	Not Exceeded	1.08	0.34	Not Exceeded
	3.21	Herbivore (long grass)	0.23	0.07	Not Exceeded	0.66	0.21	Not Exceeded
	3.21	Herbivore (broadleaf plants)	0.35	0.11	Not Exceeded	1.00	0.31	Not Exceeded
Large Sized Mammal (1 kg)								
Reproduction	3.21	Herbivore (short grass)	0.20	0.06	Not Exceeded	0.58	0.18	Not Exceeded

Table 8 **Toxic Substances Management Policy Considerations – Comparison to TSMP Track 1 Criteria**

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Combined residues of CGA 184927 and CGA 193469 Endpoints
CEPA-toxic or CEPA-toxic equivalent[1]	Yes		CGA 184927 and CGA 193469 can be considered toxic to terrestrial vascular plants
Predominantly anthropogenic[2]	Yes		N/A
Persistence[3]	Soil	Half-life ≥ 182 days	DT$_{50}$ of 20.9 to 2824 days in aerobic and anaerobic soil.
	Water	Half-life ≥ 182 days	DT$_{50}$ of (21.4, 137 and 327) to 2060 days in the water phase of aerobic and anaerobic water-sediment systems. Total system DT$_{50}$ values range from (50.9, 53.1 and 69.1) to 681 days in aerobic and anaerobic water-sediment systems.
	Sediment	Half-life ≥ 365 days	DT$_{50}$ of (56.3, 62.7 and 64.5) to 919 days in the sediment phase of aerobic and anaerobic water-sediment systems. Total system DT$_{50}$ values range from (50.9, 53.1 and 69.1) to 681 days in aerobic and anaerobic water-sediment systems.
	Air	Half-life ≥ 2 days or evidence of long range transport	Volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on **CGA 184927**: Vapour pressure (3.19×10^{-6} Pa at 25°C) and Henry's law constant (2.8×10^{-4} Pa m^3/mol at 20°C). **CGA 193469**: Vapour pressure = 7×10^{-07} Pa Henry's law constant = $<3.9 \times 10^{-10}$ Pa m^3/mol

TSMP Track 1 Criteria	**TSMP Track 1 Criterion value**	**Combined residues of CGA 184927 and CGA 193469 Endpoints**	
Bioaccumulation[4]	Log $K_{ow} \geq 5$	3.90 at 25°C for CGA 184927; -0.44 at 25°C for CGA 193469; Criteria not met, Residues not expected to bioaccumulate	
	BCF $\geq$ 5000	No data available	Not available
	BAF $\geq$ 5000	No data available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No	No

[1] All pesticides will be considered CEPA-toxic or CEPA-toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one medium (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (for example, BAFs) are preferred over laboratory data (for example,, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

Appendix VIII

Expected Environmental Concentrations (EECs)

Soil

EECs in soil were calculated based on the maximum, labelled single application rate of 70.2 g a.i./ha, for use on wheat, is made to bare soil using ground application (medium spray; 6% drift) and aerial application (coarse spray; 17% drift) with a soil bulk density of 1.5 g/cm^3 and that it is mixed evenly to a depth of 15 cm.

Table 1 **Initial EECs of clodinafop – propargyl (CGA 184927) in Soil Following a Single Application to Wheat using ground and aerial application methods.**

Crop	CGA 184927 Application Rate* g a.i./ha applied once per season using ground application	CGA 184927 EEC in soil Direct Overspray (mg a.i./kg soil)	CGA 184927 EEC in soil Spray Drift of 6% for medium spray ground boom (mg a.i./kg soil)	CGA 184927 EEC in soil Spray Drift of 17% for coarse aerial spray (mg a.i./kg soil)
Wheat (spring,durum)	70.2	0.031	0.0019	0.005

Vegetation and other food sources

EECs for CGA 184927 on wildlife food sources were estimated based on correlations in Hoerger and Kenaga (1972) and Kenaga (1973), and modified according to Fletcher et al. (1994). The EECs were determined for both on-field and off-field exposure. The highest CGA 184927 application rate was chosen to calculate screening level EECs (wheat: 70.2 g a.i./ha). A default 10-d foliar half-life was applied to the EEC for all food items. At the screening level, the EECs on food sources were based on the maximum Kenaga values at the maximum, single application rate for CGA 184927 are provided in Appendix VIII, Table 2.

Table 2 **Screening Level EECs (mg a.i./kg dw) in vegetation (foliar half-life = 10 d) and insects after a direct over-spray at 70.2 g a.i./ha) of clodinafop-propargyl (CGA 184927) on field**

Short range grass	Long grass	Broadleaf plants	Pods with seeds	Insects	Grain and seeds	Fruit
49.58	30.27	45.87	3.56	22.41	3.47	6.94

Water

EECs as a result of overspray into a body of water were calculated using the assumption that the water body has received a direct application of CGA 184927 and it has mixed evenly in a 80 cm or 15 cm depth of water (Appendix VIII, Table 3). An initial EEC immediately following a single application was calculated as a conservative measure.

Table 3 Initial EECs of clodinafop-propargyl (CGA 184927) in Water – Direct Overspray

Crop	CGA 184927 Appl. Rate* 70.2 g a.i./ha × at 1 seasonal application	Water Depth (cm)	CGA 184927 EEC in water Direct Overspray (mg a.i./L)	CGA 184927 EEC in water Spray Drift[a] (mg a.i./L)	CGA 184927 EEC in water Spray Drift[b] (mg a.i./L)
Wheat	70.2	15	0.0087	0.000522	0.001479
Wheat	70.2	80	0.046	0.00276	0.00782

[a]Based on ground boom sprayer application with medium spray quality (ASAE) spray drift is calculated at 6% of the application rate; [b]Based on aerial sprayer application with coarse spray quality (ASAE) spray drift is calculated at 17% of the application rate.

Appendix IX Label Amendments for Products Containing Clodinafop-propargyl

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements below.

The labels of end-use products registered in Canada must be amended to include the following statements:

I) Label Statements for Clodinafop-Propargyl Technical Products.

Before STORAGE section, Add the title "ENVIRONMENTAL HAZARDS" and the following statement:

- TOXIC to non-target terrestrial plants
- TOXIC to aquatic organisms

II) For Commercial and Agricultural Class Products Containing Clodinafop-propargyl

General Health Label Improvements

The following label statements are proposed to be added to the **PRECAUTIONS** of all commercial end-use product labels, unless already present:

"Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings."

Personal Protective Equipment

- Label statements must be amended (or added) to include the following directions to the appropriate labels, unless the current label mitigation is more restrictive:

Add:

"If mixing and loading more than 15 kg a.i. in a day, workers must use a closed mixing/loading system."

Remove:

"Wear coveralls or long sleeved shirt and long pants, chemical resistant gloves, and goggles when mixing loading or during equipment clean up or repair."

Replace With:

"During mixing, loading, clean-up, repair and when applying by groundboom, workers must wear coveralls over long-sleeved shirt and long pants, shoes and socks, goggles, and chemical-resistant gloves. When applying by aerial application, pilots must wear long-sleeved shirt and long pants."

Remove:

"During mixing, loading, application, spill clean-up, and sprayer clean-up, maintenance or repair, wear a long-sleeved shirt, long pants and chemical resistant gloves."

Replace With:

"During mixing, loading, clean-up, repair and when applying by groundboom, workers must wear coveralls over long-sleeved shirt and long pants, shoes and socks, and chemical-resistant gloves. When applying by aerial application, pilots must wear long-sleeved shirt and long pants."

Restricted-Entry Interval

- Label statements must be amended (or added) to include the following directions to the appropriate labels, unless the current label mitigation is more restrictive:

"DO NOT enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours."

Directions For Use

- Add:

"A 30-day plant-back interval must be observed for all unlabelled crops."

- Current label restrictions for grazing of livestock on treated crops must be amended for the appropriate labels as follows:

Remove:

"Observe a minimum of three (3) days before grazing livestock on treated crops"

Replace With:

"Observe a minimum pre-harvest interval of 60 days after treatment for grain and straw and of 30 days after treatment for hay. Observe a minimum of seven (7) days before grazing livestock on treated crops".

Add the following to ENVIRONMENTAL HAZARDS:

- **TOXIC** to non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.

- **TOXIC** to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE.
- The residues of this product demonstrate the properties and characteristics associated with chemicals detected in ground water. The use of clodinafop-propargyl products in areas where soils are permeable, particularly where the water table is shallow, may result in ground water contamination.
- To reduce runoff from treated areas into aquatic habitats, avoid application to areas with a moderate to steep slope, compacted soil or clay.
- Avoid application when heavy rain is forecast.
- Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

Add to DIRECTIONS FOR USE

The following statement is required for all agricultural and commercial pesticide products:

- As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests
- DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

Remove the following statement under the STORAGE section of the labels for the end-use products:

> "Store the product in closed original container in a well-ventilated room. Keep out of reach of children, unauthorized persons and animals. To prevent contamination store this product away from food, feed, and fertilizer."

And replace it with the following statement:

> "To prevent contamination store this product away from food or feed."

The following statement is required under the ENVIRONMENTAL PRECAUTIONS section of the label for all clodinafop-propargyl end-use products that contain aromatic petroleum distillates (PCP #s that do not contain petroleum distillates: 29089, 29614, 30341 and 30426):

> "This product contains an active ingredient and aromatic petroleum distillates which are toxic to aquatic organisms."

Add to ENVIRONMENTAL PRECAUTIONS:

TOXIC to aquatic organisms and non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.

Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) coarse classification. Reduce drift caused by turbulent wingtip vortices. The nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing- or rotorspan.

Buffer zones:

Spot treatments using hand-held equipment **DO NOT** require a buffer zone.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands) and sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands).

Method of application	**Crop**		**Buffer Zones (metres) Required for the Protection of:**		
			Freshwater Habitat of Depths:		**Terrestrial Habitat:**
			Less than 1 m	**Greater than 1 m**	
Field sprayer	Spring and durum wheat		1	0	1
Aerial	Spring and durum wheat (55.2-70.2 g a.i./ha)	Fixed wing	1	0	20
		Rotary wing	1	0	20
	Spring and durum wheat (30 g a.i./ha) (PCP 29855 and 31674)	Fixed wing	1	0	15
		Rotary wing	1	0	15

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency website.

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A. Information Considered in the Chemistry Assessment

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1915166 Part 2, DACO: 2.0,2.1,2.11.3,2.13.4,2.14,2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14,2.14.2,2.14.3, 2.14.4, 2.14.5,2.14.6,2.14.7,2.14.8,2.14.9,2.2, 2.3,2.3.1,2.4,2.5,2.6,2.7,2.8,2.9 CBI

2515029 2015, [CBI Removed] manufacturing process +discussion of impurities;, DACO: 2.11.1,2.11.2,2.11.3,2.11.4 CBI

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2560830 2015, List of startig materials, DACO: 2.11.2 CBI

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2069548 2011, Supplementary Data for the Registration of the Pesticide Clodinafop-propargyl Sinon Technical Active Ingredient, DACO: 2.11.2 CBI

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1595874 2003, Chemical Composition of CGA184927 tech., DACO: 2.13.3

2373438 2013, Clodinafop-propargyl Technical (CGA184927)- Document J, DACO: 0.8.11,0.8.12,2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.12.2,2.13.3,2.13.4,2.2,Document J,IIA 1.10.1,IIA 1.10.2,IIA 1.11.1,IIA 1.11.2,IIA 1.2,IIA 1.8.1,IIA 1.8.2,IIA 1.9.1,IIA 1.9.2,IIA 1.9.3,IIA 4.2.3,IIA 4.2.4 CBI

1429188 2006, Clodinafop-Propargyl Technical - Five Lots Analysis and Method Validation, DACO: 2.13.1,2.13.2,2.13.3,2.14.12 CBI

2432148 2014, Clodinafop-Propargyl Technical - Five Lots Analysis and Method Validation, DACO: 2.13.1,2.13.2,2.13.3,2.13.4 CBI

2432149 2014, Clodinafop-Propargyl Technical - Five Lots Analysis and Method Validation;[CBI removed], DACO: 2.13.1,2.13.2,2.13.3,2.13.4 CBI

1619833 2007, PRELIMINARY ANALYSES OF FIVE REPRESENTATIVE PRODUCTION BATCHES OF CLODINAFOP-PROPARGYL TECHNICAL GRADE ACTIVE INGREDIENT (TGAI) TO DETERMINE % CLODINAFOP-PROPARGYL AND TO QUANTIFY ITS ASSOCIATED IMPURITIES, DACO: 2.12,2.12.1,2.13,2.13.1,2.13.2,2.13.3 CBI

1587523 2007, Preliminary Analyses of Five Reprsentative production Batches of Clodinafop-propargyl technical grade active ingredinet (TGAI) to determine % clodinafop-propargyl and to quantify its assocaited impurities, DACO: 2.13.2,2.13.3

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2515030 2014, Identification and determination of active ingredient Clodinafop-Propargyl (CAS No. 105512-06-9) and impurities in five samples of Clodinafop-Propargyl Technical, Batch Nos.: 131/13, 132/13, 133/13, 134/13 and 135/13., DACO: 2.13.2,2.13.3 CBI

1991970 2009, Five Batches Analysis of Technical Grade Active Ingredient (TGAI) Clodinafop-propargyl, DACO: 2.13.1,2.13.2,2.13.3,2.13.4,2.14.12 CBI

2077712 2011, Purity Profile Study of 5 Batches of Clodinafop propargyl Technical, DACO: 2.12,2.12.1,2.13,2.13.1,2.13.2,2.13.3 CBI

2173705 2012, Preliminary Analysis Testing of Hydroquinone in Clodinafop Propargyl Technical, DACO: 2.13.4 CBI

2768723 2015, ANALYSIS OF FIVE REPRESENTATIVE PRODUCTION BATCHES OF CLODINAFOP-PROPARGYL GRADE ACTIVE INGREDIENT (TGAI) TO DETERMINE % CLODINAFOP-PROPARGYL AND TO QUANTIFY ITS ASSOCIA TED IMPURITIES, DACO: 2.13.1,2.13.2,2.13.3,2.13.4 CBI

2761131 2014, Clodinafop-propargyl - 5 Batch Analysis [Privacy removed], DACO: 2.13.3 CBI

2761132 2017, Clodinafop-propargyl - solvents 5 Batch Analysis [Privacy removed], DACO: 2.13.4 CBI

2761133 2017, Clodinafop-propargyl - solvents 5 Batch Analysis [Privacy removed], DACO: 2.13.4 CBI

2670984 2015, Quality Control Data for Clodinafop-propargyl ADAMA [Privacy removed], DACO: 2.13.3 CBI

2670985 2008, Determination of [CBI removed] in Clodinafop - Propargyl Technical Five Lot Analysis amd Method Validation, DACO: 2.13.4 CBI

2670986 2015, Determination of [CBI removed] Residue in Five Batches of Clodinafop - Propargyl Technical and Specificity of Impurities Profile Analytical Method, DACO: 2.13.4 CBI

2670987 2016, [CBI removed] Analysis in Clodinafo-propargyl Technical, DACO: 2.13.4 CBI

2670988 2016, [CBI removed] Analysis in Clodinafo-propargyl Technical, DACO: 2.13.4 CBI

2717009 2016, Determination of [CBI removed] in five batches ofClodinafop-Propargyl Technical, DACO: 2.13.4 CBI

2692487 2016, Five Batches Analysis of Technical Grade Active Ingredient (TGAI) Clodinafop-propargyl, DACO: 2.13.3 CBI

2761508 2017, Five batch report of clodinafop-propargyl technical, DACO: 2.13.3 CBI

2761509 2017, Five batch report of clodinafop-propargyl technical, DACO: 2.13.3 CBI

B. Information Considered in the Toxicological Assessment

Toxicology

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1447502	1999, CGA-193469 (free acid derivative of CGA-184927) peroxisome proliferators: species differences in the regulation of gene expression, DACO 4.8
1447503, 1451494	1999, Effects on selected plasma hormone concentrations and biochemical parameters in the liver upon subchronic administration to male adult rats, DACO 4.8
1447504	1998, Cattley, RC, et al. (1998) Regulatory Toxicology and Pharmacology. Do peroxisome proliferating compounds pose a hepatocarcinogenic hazard to humans?, DACO 4.8
1128922	1992, Note to reviewer: summaries: clodinafop-propargyl- evaluation CGA 184927 toxicology and safety assessment, DACO 4.1
1169367	1991, Toxicology summaries - preliminary evaluation (CGA 184927: toxicology and safety assessment), DACO 4.1
1128883	1991, Acute oral toxicity in the mouse (clodinafop-propargyl), DACO 4.2.1
1169346	1987, Final report, CGA 184927, acute oral toxicity in the rat, DACO 4.2.1
1169347	1987, Acute dermal toxicity study of clodinafop-propargyl technical in rats, DACO 4.2.2
1169348	1987, Acute inhalation toxicity study of clodinafop-propargyl technical in rats, DACO 4.2.3
1169349	1987, Acute eye irritation study of clodinafop-propargyl technical in rabbits, DACO 4.2.4
1169350	1987, Acute dermal irritation study of clodinafop-propargyl technical in rabbits, DACO 4.2.5
1169351	1987, Skin sensitisation study of clodinafop-propargyl technical in guinea pigs, DACO 4.2.6
2346275	2007, Effects on liver cell proliferation upon subchronic oral (feeding) administration to male mice, DACO 4.8
1239446	1988, Final report, CGA 184927 tech. 28-day oral cumulative toxicity study in rats (gavage), DACO 4.3
1239447	1989, Final report, CGA 184927 tech. 3-month oral toxicity study in rats (administration in food), DACO 4.3.1
1451477	1989, 3-month oral toxicity study in mice (administration in food), DACO 4.3.1
1239450	1987, 13-week oral toxicity (feeding) study with CGA 184927 in the dog, DACO 4.3.2
1239451, 1156319	1989, CGA 184927 tech. oral toxicity 52-week feeding study in dogs, DACO 4.3.2
1451479	2003, Clodinafop-propargyl: 28 day range-finding dietary toxicity study in rats, DACO 4.3.3

PMRA Document Number	Reference
1239452	1989, Final report, CGA 184927, 28-day repeated dose dermal toxicity in the rat, DACO 4.3.5
1128917, 1169366	1991, Determination of residues as CGA 193469 in abdominal fat after a 3-month oral toxicity study in rat (clodinafop-propargyl), DACO 4.3.8
1123424, 1123353, 1158474	1992, Final report, CGA 184927 tech. 18-month carcinogenicity study in mice, DACO 4.4.1, 4.4.2
1128894	1992, CGA 184927 technical: 24-month carcinogenicity and chronic toxicity study in rats final report (clodinafop-propargyl), DACO 4.4.1, 4.4.2
1158474	1992, Response to questions by food directorate: list of criteria utilized by the pathologist in determining the grading system for histopathological lesions in the 18-month carcinogenicity study in mice (clodinafop-propargyl), DACO 4.4.1, 4.4.2
1451480	2002, Pathology working group (PWG) peer review of proliferative lesions of the ovary in female rats in a 24-month carcinogenicity and chronic toxicity study of CGA 184927 technical, DACO 4.4.4
1451482	2002, Pathology work group (PWG) peer review of proliferative lesions of the prostate in male rats in a 24-month carcinogenicity and chronic toxicity study of CGA 184927 technical, DACO 4.4.4
1451483	2005, Clodinafop-propargyl (CGA 184927): additional prostate historical control data requested by the USEPA for the two-year carcinogenicity study in rats, DACO 4.4.4
1128920, 1169368	1991, Determination of residues as CGA 193469 in abdominal fat after 12-months in study (clodinafop-propargyl), DACO 4.4.5
1128921, 1169369	1991, Determination of residues as CGA 193469 in abdominal fat after a lifetime carcinogenicity and chronic toxicity study in rats (clodinafop-propargyl), DACO 4.4.5
2529343	2015, Response to clarification, DACO 4.5
2542272	2015, Response to clarification, DACO 4.5
1239131	1991, Final report, CGA 184927 tech. two generation oral (dietary administration) reproduction toxicity study in the rat (one litter per generation), DACO 4.5.1
1128906	1993, Reproduction toxicity in the rat on CGA 184927 technical (one litter per generation) - in response to questions (clodinafop-propargyl), DACO 4.5.1
1451488	2003, Clodinafop-propargyl: preliminary acute neurotoxicity study in rats, DACO 4.5.12
1451489	2003, Clodinafop-propargyl: acute neurotoxicity study in rats, DACO 4.5.12
2529344	2015, Historical control data description 1998 to 2006, DACO 4.5.12
2529345	2015, Acute neurotoxicity study in rats, historical control data for forelimb grip strength 1998 to 2006, DACO 4.5.12
2529346	2015, Acute neurotoxicity study in rats - HCD pathology, DACO 4.5.12
2529347	2003, Acute neurotoxicity study in rats - motor activity SOP, DACO 4.5.12
2542273	2007, Acute neurotoxicity study in rats - Standard operating procedure - functional observation battery, DACO 4.5.12
1451490	2003, Clodinafop-propargyl: subchronic neurotoxicity study in rats, DACO 4.5.13
2529348	2015, Historical control data for subchronic neurotoxicity study - list 1998 to 2006, DACO 4.5.13

PMRA Document Number	Reference
2529349	2015, Historical control data for subchronic neurotoxicity study - time to tail flick, DACO 4.5.13
2529350	2015, Historical control data for subchronic neurotoxicity study – demyelination, DACO 4.5.13
1451491	2003, Clodinafop-propargyl: preliminary developmental neurotoxicity study in rats, DACO 4.5.14
1451492	2003, Clodinafop-propargyl: developmental neurotoxicity study in rats. DACO 4.5.14
1451493	2007, Supplement to developmental neurotoxicity study in rats, DACO 4.5.14
2529351	2003, Developmental neurotoxicity study in rats, Motor activity - positive control study, DACO 4.5.14
2529352 2529353	2015, Historical control for Developmental neurotoxicity study in rats - study list, DACO 4.5.14
2529354, 2529356	2015, Historical control for Developmental neurotoxicity study in rats - pathology, DACO 4.5.14
2529355	2003, Developmental neurotoxicity study in rats - Learning & memory positive control, DACO 4.5.14
2542274	2006, Developmental neurotoxicity study in rats, Standard operating procedure - startle reflex system, DACO 4.5.14
2542275	2003, Standard operating procedure - maze to assess learning and memory in rats and mice, DACO 4.5.14
1158416	1988, Dose-range finding study in the pregnant rat by the oral route final report (clodinafop-propargyl), DACO 4.5.2
1239120	1988, Final report, CGA 184927 tech. teratology study in the rat by oral route, DACO 4.5.2
1239109	1988, Final report, CGA 184927 tech. teratology study in the rabbit by oral route, DACO 4.5.3
1158417	1993, Individual data on clinical symptoms, resorptions, and the observations at the caesarean sections. Supplement to teratology study in the rabbit by the oral route (clodinafop-propargyl), DACO 4.5.2
1158475	1992, Responses to questions from food directorate: statement of age of rats, and individual data on clinical symptoms, resorptions, and the observations at the caesarean sections. Supplement to teratology study in rat by oral route. (clodinafop-propargyl), DACO 4.5.2
2346276	2008, Salmonella typhimurium and Escherichia coli reverse mutation assay, DACO 4.5.4
2349849, 1239140	1987, CGA-184972: Salmonella/mammalian-microsome mutagenicity test (OECD-conform) - test no. 871022, DACO 4.5.4
2350865	2005, Mutagenicity evaluation of clodinafop propargyl technical by Ames Salmonella typhimurium - reverse mutation assay, DACO 4.5.4
2350867	2012, Amended report: reverse mutation assay using bacteria (salmonella typhimurium and Escherichia coli) with clodinafop-propargyl technical, DACO 4.5.4
1451484	2000, Cytogenetic test on Chinese hamster cells in vitro, DACO 4.5.6
1239143	1988, Report, point mutation test with Chinese hamster cells V79 (OECD conform), DACO 4.5.6

PMRA Document Number	Reference
1239141	1987, Report, autoradiographic DNA-repair test on rat hepatocytes (OECD-conform)
2349851, 1239142	1987, CGA 184927 tech - micronucleus test (mouse), DACO 4.5.7
2350868	2005, Mutagenicity evaluation of clodinafop propargyl technical - mouse bone marrow cytogenetic assay (chromosomal aberration), DACO 4.5.7
2350869	2005, Mutagenicity evaluation of clodinafop propargyl technical - mouse micronucleus assay, DACO 4.5.7
1451487	1999, In vivo/in vitro unscheduled DNA synthesis in rat hepatocytes, DACO 4.5.8
2346277	2007, In vitro assessment of the clastogenic activity of clodinafop-propargyl technical in cultured CHO cells, DACO 4.5.8
2346278	2007, Unscheduled DNA synthesis test of clodinafop-propargyl technical by oral administration to cd rates in vivo/in vitro study, DACO 4.5.8
2349853	1999, In vivo/in vitro unscheduled DNA synthesis in rat hepatocytes, DACO 4.5.8
2350871	2006, Mutagenicity evaluation of clodinafop propargyl technical by dominant lethal test in mouse, DACO 4.5.8
1239144	1988, Report, chromosome studies on human lymphocytes in vitro, DACO 4.5.8
1128923	1992, Effects of CGA 193469, the free acid derivative of CGA 184927 on peroxisomal β-oxidation in human hepatocytes (clodinafop-propargyl), DACO 4.8
1451495	1999, Peroxisome proliferators: species differences in the regulation of gene expression, DACO 4.8
1451496	2001, Effects on biochemical parameters in the liver upon subchronic administration to male mice, DACO 4.8
1451497	2002, Quantitative assessment of the peroxisomal compartment in liver cells of rats treated with clodinafop-propargyl (CGA 184927) - a retrospective study, DACO 4.8
1451498	2002, Assessment of hepatic peroxisome proliferation in male mice upon treatment for 28 days with CGA 184927 (clodinafop-propargyl), DACO 4.8
1451499	2001, Assessment of hepatic cell proliferation in male mice upon treatment with CGA 184927 for up to 28 days, DACO 4.8
1451500	1998, Degradation of CGA 184927 in rat plasma, DACO 4.8
1451501	2003, Clodinafop-propargyl (CGA-184927): rodent tumors and their relevance to human health risk assessment, DACO 4.8
1451502	2003, Clodinafop-propargyl (CGA-184927): assessment of the need for the use of an additional uncertainty factor to address the potential for increased susceptibility of infants and children, DACO 4.8
1451503	2003, Motor activity: positive control study in rat pups, DACO 4.8
1451504	2003, Positive control study for grip strength, DACO 4.8
1451505	2004, Positive control study for neurotoxicology and neuropathology in adult rats, DACO 4.8
1451506	2004, Positive control study for brain morphometry in rat pups, DACO 4.8
1451507	1996, Trimethyltin chloride: investigation of neurotoxicity in rat pups using morphometrics and startle response, DACO 4.8
1239453	1991, The effect of CGA 193469, the free acid derivative of CGA 184927, on peroxisomal β-oxidation in primary cultures of rat, mouse, marmoset and guinea pig hepatocytes, DACO 4.8

B. Additional Information Considered

i) Published Information

PMRA Document Number	Reference
1447501	1995, UK review (1995) Food and Environment Protection Act, 1985, Part III, Control of Pesticides Regulations 1986, Evaluation of fully approved or provisionally approved products, evaluation on: clodinafop-propargyl and cloquintocet-mexyl, DACO 12.5
1447504	1998, Cattley, RC, et al. (1998) Regulatory Toxicology and Pharmacology. Do peroxisome proliferating compounds pose a hepatocarcinogenic hazard to humans?, DACO 4.8
2525430, 2248578	2005, EFSA Scientific Report. Conclusion regarding the peer review of the pesticide risk assessment of the active substance clodinafop, DACO 12.5
2525437	2006, European Commission. Final review report for the active substance clodinafop finalised in the standing committee on the food chain and animal health at its meeting on 27 January 2006 in view of the inclusion of clodinafop in annex I of directive 91/414/EEC, DACO 12.5
1447500	1995, Australian NRA review (1995) public release summary of the evaluation by the NRA of the new active constituents: clodinafop-propargyl and cloquintocet-mexyl in the product: Topik selective herbicide, DACO 12.5, 12.5.7
2801852	2004, European Commission, Draft Renewal Assessment (DAR) – public version – Initial risk assessment provided by the rapporteur Member State The Netherlands for the existing active substance clodinafop (based on the variant clodinafop-propargyl), Volume 3, Annex B, B.6, part 1, DACO 12.5.4
2801853	2004, European Commission, Draft Renewal Assessment (DAR) – public version – Initial risk assessment provided by the rapporteur Member State The Netherlands for the existing active substance clodinafop (based on the variant clodinafop-propargyl), Volume 3, Annex B, B.6, part 2, DACO 12.5.4
2801853	2004, European Commission, Draft Renewal Assessment (DAR) – public version – Initial risk assessment provided by the rapporteur Member State The Netherlands for the existing active substance clodinafop (based on the variant clodinafop-propargyl), Volume 3, Annex B, B.6, part 3, DACO 12.5.4
2801855	2011, EFSA – Reasoned Opinion, review of the existing maximum residue levels (MRLs) for clodinafop according to Article 12 of Regulation (EC) No 396/2005, DACO 12.5
2801856	2000, USEPA (U.S. Environmental Protection Agency), – PP#7F04924. Human Health Risk assessment for the use of the new active ingredient, clodinafop-propargyl, on wheat, DACO 12.5
2801857	2012, USEPA (U.S. Environmental Protection Agency), – Clodinafop-propargyl. Human health risk assessment for clodinafop-propargyl to reduce the established tolerance on wheat grain, DACO 12.5

PMRA Document Number	Reference
2801858	2012, USEPA (U.S. Environmental Protection Agency),, clodinafop-propargyl, human health assessment scoping document in support of registration review, DACO 12.5
2801861	2000, USEPA (U.S. Environmental Protection Agency),, PP7F04924, clodinafop-propargyl (PC Code: 125203), toxicology disciplinary chapter for registration support document, DACO 12.5.4
2801859	2003, USEPA (U.S. Environmental Protection Agency), proposed OPPTS Science Policy: PPARα-mediated hepatocarcinogesis in rodents and relevance to human health risk assessments.
2801860	2003, Klaunig JE, et al. PPARα agonist-induced rodent tumors: modes of action and human relevance. Critical Reviews in Toxicology. Vol 33 (6): 655-780. Available online from http://www.tandfonline.com/doi/abs/10.1080/713608372 [last accessed July, 2017]
TBD	2017, European Commission, Renewal Assessment Report (RAR) – public version – Initial risk assessment provided by the rapporteur Member State The Greece for clodinafop (based on the variant clodinafop-propargyl), Volume 3, Annex B, B.6, DACO 12.5.4
TBD	2017, European Commission, Draft Renewal Assessment (DAR) – public version – Initial risk assessment provided by the rapporteur Member State Greece for clodinafop (based on the variant clodinafop-propargyl), List of endpoints, DACO 12.5.4

ii) Unpublished Information

PMRA Document Number	Reference
2801862	1994, Health and Welfare Canada, Health Protection Branch, Health and Safety Status Report, Clodinafop-propargyl.
2801863	1999, USEPA, (U.S. Environmental Protection Agency), Clodinafop-propargyl (CGA 184927) – Report of the Cancer Assessment Review Committee, DACO 12.5.4
2801865	2008, USEPA (U.S. Environmental Protection Agency), Data Evaluation Record, subchronic neurotoxicity – Rats, DACO 12.5.4
2801866	2004, USEPA (U.S. Environmental Protection Agency), Data Evaluation Record, acute neurotoxicity – Rats, DACO 12.5.4
2801864	2006, USEPA (U.S. Environmental Protection Agency), Clodinafop-propargyl: second report of the cancer assessment review committee, DACO 12.5.4
2801867	1999, USEPA (U.S. Environmental Protection Agency), Clodinafop-propargyl (CGA 184927): Report of the hazard identification assessment review committee, DACO 12.5.4
2801868	1998, USEPA (U.S. Environmental Protection Agency), Data Evaluation Record, chronic/carcinogenicity study, DACO 12.5.4
2801869	2000, USEPA (U.S. Environmental Protection Agency), Memorandum, Revised CGA 184927 (clodinafop-propargyl) quantitative risk assessment (Q_1*) based on

PMRA Document Number	Reference
	Tif:RAIf(SPF) Albino Rat and Tif:MAGf(SPF) Albino Mouse chronic dietary studies with 3/4 ‘s interspecies scaling factor

C. Information Considered in the Dietary Assessment

A. Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1128874	1991. Outdoor Confined Accumulation Study on Rotational Crops after Applicationss of CGA-184927 (2-14C-Pyridyl) (Clodinafop-propargyl)
1128877	1990. Determination of Residues of Parent Compounds by Liquid Chromatography (Clodinafop-propargyl)
1128878	1990. Determination of Residues of Metabolite CGA-193469 by Liquid Chromatography (HPLC) (Clodinafop-propargyl)
1128879	1991. Determination of Residues of Metabolite CGA-193469 by Liquid Chromatography (Clodinafop-propargyl)
1128880	1991. Determination of Residues of Metabolites CGA-153433 and CGA-193469 by Liquid Chromatography (Clodinafop-propargyl)
1128881	1993. Determination of Residues of CGA-184927, CGA-185072 and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial (Clodinafop-propargyl)
1128882	1993. Determination of Residues of CGA-184927, CGA-185072 and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial (Clodinafop-propargyl)
1128884	1993. Determination of Residues of CGA-184927, CGA-185072 and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial (Clodinafop-propargyl)
1128885	1992. Determination of Parent Compounds and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial (Clodinafop-propargyl)
1128886	1992. Determination of Parent Compounds and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial (Clodinafop-propargyl)
1128887	1992. Determination of Parent Compounds and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial (Clodinafop-propargyl)
1128888	1992. Determination of Residues of CGA-184927, CGA-185072 and Metabolites CGA-193469 and CGA-153433 in Wheat (Green Forage) - Field Trial (Clodinafop-propargyl)
1128889	1992. Determination of Residues of CGA-184927, CGA-185072 and Metabolites CGA-193469 and CGA-153433 in Wheat (Green Forage) - Field Trial (Clodinafop-propargyl)

PMRA Document Number	Reference
1128890	1992. Determination of Residues of CGA-184927, CGA-185072 and Metabolites CGA-193469 and CGA-153433 in Wheat (Green Forage) - Field Trial (Clodinafop-propargyl)
1128891	1991. Determination of Residues of Parent Compounds and Metabolites CGA-193469 and CGA-153433 in Wheat (Grain and Straw) - Field Trial (Clodinafop-propargyl)
1128892	1991. Determination of Residues of Parent Compounds and Metabolites CGA-193469 and CGA-153433 in Wheat (Grain and Straw) - Field Trial (Clodinafop-propargyl)
1128893	1991. Determination of Residues of Parent Compounds and Metabolites CGA-193469 and CGA-153433 in Wheat (Grain and Straw) - Field Trial (Clodinafop-propargyl)
1128896	1990. Residue Determination of CGA-193469 (Major Metabolite of Herbicide CGA-184927) in Wheat (Grain) After Single Application of 100EC (Clodinafop-propargyl)
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4.0 Impact on the Environment

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B. ADDITIONAL INFORMATION CONSIDERED

i) Published Information

4.0 Environment

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